

**PROTOCOL EP0069 AMENDMENT 4.0**

**A DOUBLE-BLIND, RANDOMIZED,  
PLACEBO-CONTROLLED STUDY OF THE EFFICACY,  
SAFETY/TOLERABILITY, AND PHARMACOKINETIC  
PROFILE OF UCB0942 IN ADULT PATIENTS WITH HIGHLY  
DRUG-RESISTANT FOCAL EPILEPSY**

**PHASE 2A**

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Sponsor:

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## LIST OF ABBREVIATIONS

50%RR	50% responder rate
75%RR	75% responder rate
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BPRS	Brief Psychiatric Rating Scale
BRV	brivaracetam
BUN	blood urea nitrogen
cBZR	benzodiazepine-binding site
CDMS	clinical data management system
CI	confidence interval
CIWA-B	Clinical Institute Withdrawal Assessment-Benzodiazepines
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DAP	data analysis plan
DNA	deoxyribonucleic acid
DS	Drug Safety
ECG	electrocardiogram
eCRF	electronic Case Report form
EEG	electroencephalogram
EPM	Exploratory Project Manager
ES	Enrolled Set

EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
GABA-A	gamma-aminobutyric acid receptor type A
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C antibody
HIV-1/2Ab	human immunodeficiency virus-1/2 antibody
ICF	Informed Consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRT	interactive response technology
LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMSE	mini-mental state examination
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCA	non-compartmental analysis
OLE	open-label extension
PDILI	potential drug-induced liver injury
PI	Principal Investigator
PK	pharmacokinetic(s)
PPS	Per-Protocol Set
QOLIE-31-P	Quality of Life Inventory in Epilepsy-31-P
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RS	Randomized Set
SAE	serious adverse event
SD	standard deviation
SFU	Safety Follow Up
SAP	Statistical Analysis Plan

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SOP	Standard Operating Procedure
SRG	Safety Review Group
SS	Safety Set
SSQ	Seizure Severity Questionnaire
SV2	synaptic vesicle glycoprotein 2 (also known as SV2A)
ULN	upper limit of normal
VNS	vagus nerve stimulation

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## 1 SUMMARY

UCB0942 is a new chemical entity with selective affinity for synaptic vesicle glycoprotein 2 (SV2) and for the benzodiazepine-binding site (cBZR) on the gamma-aminobutyric acid receptor type A (GABA-A). UCB0942 has shown superior efficacy in several preclinical models of epilepsy.

EP0069 is a Phase 2A, double-blind, randomized, placebo-controlled, multicenter study that will test the potential efficacy, safety/tolerability, and pharmacokinetic (PK) profile of UCB0942 in adult subjects with highly drug-resistant focal epilepsy. Randomization will be in a 1:1 ratio.

The primary objective of the study is to evaluate the efficacy of UCB0942 administered concomitantly with each subject's current, stable antiepileptic drug (AED) regimen in subjects who have 4 or more focal seizures with or without secondary generalization per week and who have failed to achieve seizure control with  $\geq 4$  AED regimens of adequate dose and duration. In this protocol, unless otherwise specified, "focal seizures" refers to partial-onset seizures of type IA1, IB, and IC, but does *not include* type IA2, IA3, or IA4 seizures.

The secondary objectives are to evaluate the safety and tolerability of UCB0942 and to evaluate the steady-state PK of UCB0942 and its metabolites.

This study consists of:

- A 4-week prescreening Historical Baseline Period for study eligibility purposes
- A Screening Visit followed by a 2- to 3-week postscreening Prospective Outpatient Baseline Period (Day BL1 to Day BL14-21)
- A 3-week Inpatient Period which consists of:
  - An Inpatient Titration Week (Day T1 to Day T7)
  - An Inpatient Maintenance-Dose Week (Day MD1 to Day MD7)
  - An Inpatient Transition-to-Outpatient Week (Day TTO1 to Day TTO7)
- An open-label Outpatient Maintenance Period of 8 weeks (Day OP1 to Day OP57)
- A Tapering Period of 2 weeks (Day TOO1 to Day TOO14)
- A Safety Follow-Up (SFU) Period of 4 weeks (Day SFU1 to Day SFU28)
- An echocardiogram during dosing and after the last dose (the SFU7 echocardiogram). The echocardiogram will be repeated at 6 months ( $\pm 1$  month) after the last dose in the following subjects:
  - Subjects who complete this study but do not enter the OLE study
  - Subjects who withdraw from the Outpatient Period
  - Subjects who withdraw from the Inpatient Period and have an abnormal SFU7 echocardiogram

Titration to UCB0942 400mg bid will occur over the course of 1 week in the clinical unit. For subjects in the active arm, doses will be titrated to UCB0942 400mg bid during the first inpatient week. For subjects who initially received placebo, doses will be titrated to UCB0942 400mg bid during the last week of the Inpatient Period. Dose reductions will be allowed during titration and maintenance in the Inpatient Period, but this should be discussed

with the Sponsor Study Physician unless this is not possible due to the circumstances. Multiple adjustments (tapering or increase) of the dose are allowed during the Outpatient Maintenance Period (minimum 100mg bid and maximum 400mg bid); however, any change of dose in the Outpatient Maintenance Period should first be discussed with the Sponsor Study Physician.

The total duration for subject participation in the study will be up to 20 weeks, plus an echocardiographic follow-up visit 6 months after the last dose of study medication. The total duration of exposure to UCB0942 is 13 weeks in EP0069. Subjects who experience substantial benefit from UCB0942 with acceptable tolerability according to the subject and Investigator, will have the opportunity to continue taking UCB0942 in an open-label extension (OLE) study. Each subject's decision to enter the OLE study will be in consultation with their neurologist and taking into account the potential risks and benefits of continuing to take UCB0942 and the potential risks and benefits of other treatment options. Subjects who enter the OLE study will not have a Tapering Period at the end of the Outpatient Maintenance Period. The OLE study is described in a separate protocol (EP0073).

The primary efficacy measure is the 75% responder rate (75%RR, proportion of subjects who achieve  $\geq 75\%$  reduction in focal seizure frequency) during the Inpatient Period compared to the 2-week Prospective Outpatient Baseline Period.

Secondary efficacy variables include:

- Median percent reduction in weekly focal seizure frequency from the Prospective Outpatient Baseline Period to the Inpatient Period and the End of Treatment.
- Seizure-free rate during the Inpatient Period, the last 4 weeks of the Outpatient Maintenance Period, and at the End of Treatment.
- The 75%RR during the last 4 weeks of the Outpatient Maintenance Period and at the End of Treatment.
- Percentage of seizure-free days during the Inpatient and Outpatient Periods.

The exploratory efficacy variables are detailed in Section 4.1.3.

Plasma concentrations of UCB0942, and its identified metabolites [REDACTED], will be determined from blood samples obtained in the study in order to investigate the PK of UCB0942 and its major metabolites.

Blood samples for deoxyribonucleic acid (DNA), messenger ribonucleic acid (mRNA), and lipidomics/proteomics/additional blood biomarkers will be collected during the study for exploratory biomarker studies.

The safety of participating subjects will be closely monitored. Assessment of specific domains of psychiatric and cognitive symptoms will be performed by a staff member trained in the identification of psychiatric symptoms.

Other safety variables are detailed in Section 4.4.

## **2 INTRODUCTION**

### **2.1 General background**

In Europe and North America there are 350,000 to 500,000 (3 to 4 million worldwide) patients with focal epilepsy who have not been able to achieve freedom from disabling seizures despite sequential and/or combination treatment with several of the available AEDs. Despite the introduction of 12 new AEDs over the last 2 decades, the proportion of patients

with epilepsy who are unable to achieve complete control of their seizures has only decreased minimally, from 36% to 34% (Brodie et al, 2012), highlighting the large unmet medical need and the fact that recently-developed AEDs have not been able to meet this medical need.

Patients with focal epilepsy who have failed to achieve seizure control with 2 or more AED regimens are defined as drug-resistant by the International League Against Epilepsy (ILAE; Kwan et al, 2010). It is important to highlight that there is a continuum of degrees of drug resistance within the patient population classified as drug-resistant according to ILAE criteria. When a patient with focal epilepsy has failed to achieve seizure freedom after the second AED regimen, he or she has less than 10% chance of achieving complete seizure control with subsequent AED regimens (Steinhoff, 2014; Beyenburg et al, 2012; Chung et al, 2010; Schiller and Najjar, 2008; Mohanraj and Brodie, 2006). The likelihood of achieving complete seizure control diminishes as the number of failed AED regimens increases. Thus, when a patient with focal epilepsy has not been able to control their seizures despite treatment with 5 or more AED regimens, the likelihood of achieving complete seizure control with another AED regimen is 1-6% (Schiller and Najjar, 2008; Mohanraj and Brodie, 2006; UCB internal data on lacosamide and brivaracetam [BRV]). In addition, high-seizure frequency also correlates with reduced likelihood of achieving seizure freedom. For instance, patients who have failed 3 or 4 AED regimens but who have daily seizures have only a 2% chance of becoming seizure free with subsequent AEDs. In this study, to ensure that subjects who participate have a very low likelihood of benefiting from existing treatments, we will combine 2 criteria to identify the target population: failure to control seizures despite treatment with at least 4 AED regimens *and* having at least 4 seizures per week on average. This group of patients will be referred to as having “highly drug-resistant focal epilepsy.”

Resective surgery is an option for some patients with drug-resistant focal epilepsy. The ILAE recommends that patients be evaluated for surgery after failing to achieve seizure freedom with the second AED regimen; however, in most places patients are referred for surgery only after failing multiple AED regimens. Therefore, the patients who in practice are evaluated for and undergo surgery are similar to the highly drug-resistant population as defined above. Due to various factors (limited number of epilepsy surgery centers, inability to localize the seizure focus during work-up, contraindications to surgery, etc) fewer than 1% of patients with drug-resistant focal epilepsy undergo epilepsy surgery. Therefore, the vast majority of patients with highly drug-resistant focal epilepsy have no treatment options (pharmacological or surgical) that can provide complete seizure control or even substantial reduction in the number of seizures.

UCB0942 has shown superior efficacy in several preclinical models of epilepsy. UCB0942 is superior to levetiracetam (LEV) and BRV in 10 animal models of focal and generalized epilepsy, indicating that it has broad antiseizure effects. In the rat amygdala kindling model – a model of drug-resistant focal epilepsy – UCB0942 is superior to 12 other AEDs tested thus far: LEV, BRV, phenytoin, phenobarbital, carbamazepine, lacosamide, valproate, retigabine, perampanel, clobazam, diazepam, clonazepam, and the combination of LEV or BRV with diazepam. In this model of drug-resistant focal epilepsy, UCB0942 was the only compound that produced complete seizure suppression in all animals at a plasma exposure equivalent to the plasma exposure achieved in humans taking UCB0942 400mg bid. Other AEDs produced seizure suppression in this model, but only at plasma exposures that are unattainable in humans. Based on its superior preclinical efficacy profile, UCB0942 may show efficacy in patients with focal epilepsy who continue to suffer from frequent seizures despite having attempted to achieve seizure control with multiple AED regimens (patients with highly drug-resistant focal epilepsy).



If seizure freedom or a substantial reduction in seizure frequency could be achieved in these patients, their quality of life would dramatically improve, and this improvement is expected to outweigh the potential risks associated with the administration of UCB0942.

Preclinical experience with UCB0942 is described extensively in the Investigator's Brochure.

## **2.2 Phase 1 experience**

UCB0942 has completed Phase 1 development with a total of 145 subjects exposed to single doses up to UCB0942 490mg and multiple doses up to UCB0942 400mg bid for up to 14 days, including 20 subjects with epilepsy at 400mg bid. There were no clinically significant changes in laboratory tests or vital signs thought to be related to UCB0942 during Phase 1 development, although transient, minor reductions in systolic and diastolic blood pressure were seen (consistent with the known effects of benzodiazepine drugs). There were no clinically significant changes attributed to UCB0942 in 12-lead ECGs; however, 4 subjects had treatment-emergent rhythm disturbances (atrial and ventricular ectopy). These were asymptomatic and were assessed by an external cardiologist expert in electrophysiology as unlikely to be related to UCB0942.

### **2.2.1 Adverse event profile**

The safety findings to date suggest that the adverse event (AE) profile in subjects receiving single and repeated doses of UCB0942 is related mostly to the central nervous system (CNS). At UCB0942 300mg bid and above the AEs tend to be of slightly greater severity and persistence than at doses below UCB0942 300mg bid. In broad terms, the AEs are consistent with the AEs associated with established SV2 and GABA-A targeting AEDs, and common CNS AEs include headache, nausea, somnolence, fatigue, dizziness, balance disorder, disturbance in attention, and memory impairment. Modeling of the relationship between dose or plasma exposure, time, and AEs showed that 1) headache, fatigue, somnolence, balance disorder, and disturbance in attention are dose-dependent AEs; 2) tolerance develops for disturbance in attention and balance disorder; 3) tolerance does not seem to develop for fatigue, somnolence, and headache; and 4) titration will reduce the likelihood that a subject experiences most of these AEs.

### **2.2.2 Psychiatric adverse events**

In the multiple ascending dose study, 1 healthy volunteer had a "delirious syndrome" with prominent psychotic symptoms, and in a subsequent Phase 1 study, 1 healthy volunteer had "mania-like symptoms." Both of these AEs were classified as serious adverse events (SAEs) because the subjects required hospitalization. After these psychiatric SAEs occurred, close psychiatric monitoring was implemented. Therefore, when 2 other healthy volunteers began to develop "hypomania" and "aggressive state," respectively, the symptoms were discovered early, and discontinuation of UCB0942 prevented the development of these symptoms into more severe psychiatric symptoms. Based on this, it appears that close psychiatric monitoring during the first 2 weeks of dosing, and tapering and discontinuation of the drug in subjects who start to develop psychiatric AEs, will reduce the risk that subjects develop more severe psychiatric AEs or psychiatric SAEs. Therefore, in this study, daily psychiatric monitoring will be performed in all subjects for the first 2 weeks after dosing starts, and weekly thereafter. In addition, to further reduce the risk that participating subjects develop psychiatric AEs, subjects with a history of psychosis, schizophrenia, bipolar disorder, or severe unipolar depression will be excluded from this study. Lastly, based on the fact that titration has been shown to reduce the incidence of other AEs and increase the general tolerability of UCB0942, titration may also reduce the risk of psychiatric AEs.



### 2.2.3 Drug-drug interactions

A drug-drug interaction study in subjects with epilepsy showed that carbamazepine – a strong cytochrome P450 (CYP) 3A4 inducer – reduced UCB0942 plasma exposure by >85%. Therefore, subjects on carbamazepine or other strong CYP3A4 inducers (eg, phenytoin, phenobarbital, or primidone) will not be enrolled in this study because the plasma exposure may be too low to produce any therapeutic benefit.

## 2.3 Rationale for this study

This is a Phase 2A efficacy, safety, and tolerability study.

Based on the preclinical results in 10 animal models of focal and generalized epilepsy, and the predated mechanisms of action, it is almost certain that UCB0942 will have antiseizure effects in humans. The rationale for the current study is to test whether UCB0942 has unprecedented efficacy in a very severe patient population, namely in subjects with focal epilepsy who continue to suffer from frequent, almost-daily seizures despite having attempted to achieve seizure control with multiple AED regimens. In this study the efficacy of UCB0942 400mg bid in subjects with such highly drug-resistant focal epilepsy will be assessed for the first time. In this protocol, “focal seizures” refers to partial-onset seizures of type IA1, IB, and IC, but does *not include* type IA2, IA3, or IA4 seizures.

Based on analysis of similar subjects in UCB’s lacosamide and BRV databases, the placebo response is very low (after 2 weeks of treatment <7% achieved  $\geq 75\%$  reduction in seizure frequency and <2% were seizure free, and after 12 weeks of treatment <4% maintained  $\geq 75\%$  reduction in seizure frequency and 0% were seizure free); however, the placebo arm is necessary to confirm that the placebo response is equally low in the current target population and in the setting of this study (ie, inpatient) and to avoid a false positive study due to an apparent seizure frequency reduction from the Prospective Outpatient Baseline Period to the Inpatient Treatment Period.

## 3 STUDY OBJECTIVES

### 3.1 Primary objective

The primary objective is to evaluate the efficacy of UCB0942 administered concomitantly with each subject’s current, stable AED regimen in subjects who have 4 or more focal seizures with or without secondary generalization per week and who have failed to achieve seizure control with  $\geq 4$  AED regimens of adequate dose and duration.

### 3.2 Secondary objectives

The secondary objectives are to:

- Evaluate the safety and tolerability of UCB0942
- Evaluate the PK of UCB0942 and its metabolites

### 3.3 Exploratory objectives

The exploratory objectives are to:

- Identify genetic polymorphisms, gene expression patterns, plasma proteins, plasma lipids, or other plasma substances that predict or are associated with disease etiology, drug response, or tolerability
- Use video recordings, when available, to explore the effect of UCB0942 on seizure type, seizure severity, seizure duration, and duration of the postictal period

- To assess motivations, hopes and impact of seizures using a Diary Addendum

## **4 STUDY VARIABLES**

### **4.1 Efficacy variables**

#### **4.1.1 Primary efficacy variable**

Seizure frequency will be determined using subject diary cards. The subject will be instructed as to how to complete the diary, and the procedure for completing the diary will be identical during the Outpatient and Inpatient Periods.

The primary outcome measure is the 75%RR. In the active group, this is defined as the proportion of subjects with a 75% or greater reduction in focal seizure frequency during the last 2 weeks of the Inpatient Period compared to the 2-week Prospective Outpatient Baseline Period. In the placebo group, the 75%RR is defined as the proportion of subjects with a 75% or greater reduction in focal seizure frequency during the first 2 weeks of the Inpatient Period (the 2 weeks on placebo) compared to the Prospective Outpatient Baseline Period.

#### **4.1.2 Secondary efficacy variables**

The secondary efficacy variables are:

- Median percent reduction in weekly focal seizure frequency from the Prospective Outpatient Baseline Period to the Inpatient Period and the End of Treatment.
- Seizure-free rate during the Inpatient Period, the last 4 weeks of the Outpatient Maintenance Period, and at the End of Treatment.
- The 75%RR during the last 4 weeks of the Outpatient Maintenance Period and at the End of Treatment.
- Percentage of seizure-free days during the Inpatient and Outpatient Periods.

#### **4.1.3 Exploratory efficacy variables**

Exploratory efficacy variables are as follows:

- Median seizure frequency by seizure type (IA1, IB, IC) per study period: Prospective Outpatient Baseline, Titration Inpatient, 1-week Maintenance Inpatient, Transition to Outpatient, Outpatient Maintenance, and overall on-treatment period.
- The 50% responder rate (50%RR) during the Inpatient Period and during the Outpatient Maintenance Period.
- Seizure Severity Questionnaire (SSQ, Cramer et al, 2002), change from Baseline to the end of the Inpatient Period and the end of the Outpatient Maintenance Period.
- Changes in average seizure severity as calculated by the percentage of seizures that are type IC.
- Change from Baseline in score (subscale and total) of the Quality of Life Inventory in Epilepsy-31-P (QOLIE-31-P, Cramer et al, 2003)

## **4.2 Pharmacokinetic variables**

Plasma concentrations of UCB0942, [REDACTED] will be used to calculate the following PK parameters:

- $AUC_{\tau}$ : area under the plasma concentration-time curve over a dosing interval

- $C_{\max}$ : maximum observed plasma concentration
- $t_{\max}$ : time of occurrence of  $C_{\max}$
- $t_{1/2}$ : apparent terminal elimination half-life
- $C_{\text{trough}}$ : measured concentration at the end of the dosing interval at steady state

### 4.3 Exploratory variables

- Blood samples for DNA, mRNA, and lipidomics/proteomics/additional blood biomarkers will be collected during the study:
  - **DNA:** One tube for DNA isolation will be collected at the beginning of the Inpatient Period of the study. The DNA may be used to assess known variants associated with drug-resistant epilepsy or AED resistance and may be used for further genetic analyses relating to epilepsy and drug response.
  - **mRNA:** One tube will be collected on the day before the first dose of UCB0942/placebo, and 1 tube will be collected on the last day of the Inpatient Maintenance-Dose Week. The mRNA samples may be used to identify gene expression patterns that are associated with disease etiology, that predict (Baseline sample), or that are associated with (posttreatment sample) drug response.
  - **Lipidomics/proteomics/additional blood biomarkers:** One tube will be collected on the day before the first dose of UCB0942 or placebo, and 1 tube will be collected on the last day of the Inpatient Maintenance-Dose Week. These samples may be used for additional blood biomarker analysis.

All subjects will be asked to provide specific consent for these samples. Refusal to provide consent for the collection of samples for DNA, mRNA, and lipidomics/proteomics will not disqualify the subject from participating in the study.

Single archive blood samples (for potential background AED assay) will be collected at the start of titration, the end of the Inpatient Period, and at the end of the Outpatient Maintenance Period (before last dose of IMP). These samples will be collected just before the morning dose of IMP and stored for up to 1 year after the study ends.

- At the discretion of the Investigator, sites may or may not perform video or video-electroencephalogram (EEG) monitoring during parts of the Inpatient Period or during the whole Inpatient Period, depending on the infrastructure of each site, to assess seizure type, severity, duration, and the duration of the postictal period. The video data will not be used to corroborate or supplement the diary data and shall not influence the diary seizure capture by the subject.
- Responses to open questions in the Diary Addendum, including:
  - Reason for participation in the study
  - Hopes for this new treatment and fulfillment of hopes during the study
  - Baseline and change from Baseline in the impact of seizures on the patient's life

The subject will be instructed to leave any questions blank that he/she does not feel comfortable answering.

## 4.4 Safety variables

The safety of participating subjects will be closely monitored. Psychiatric assessment will be performed by a staff member trained in the identification of psychiatric symptoms, and the assessments will be performed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), which assesses various psychiatric domains including:

- Changes in mood and symptoms of depression or mania
- Changes in thinking and perception, and other symptoms of psychosis
- Changes in behavior

Other safety variables are:

- Adverse events reported by the subject and/or caregiver or observed by the Investigator or inpatient staff
- Serious adverse events
- Subject withdrawals or premature UCB0942 tapering due to AEs
- Changes in clinical laboratory test parameters
- Changes in vital sign parameters – pulse rate, blood pressure, and respiratory rate
- Changes in 12-lead electrocardiogram (ECG) parameters
- Changes in 2-dimensional Doppler echocardiography from Baseline to after Baseline (during dosing, after the last dose, and 6 months after last dose), with diastolic measurements as well as atrial volumes to identify any subtle valvular changes and to assess for pericardial effusions
- Changes in physical examination (including body weight) and neurological examination findings
- Changes in memory or cognition as assessed with the mini-mental state examination (MMSE; Folstein et al, 1975)
- Changes indicative of a hypersensitivity reaction including an AE or laboratory value (as defined below) suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) combined with at least 1 of the following: fever, rash, lymphadenopathy, or eosinophilia
  - Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
    - Eosinophils %  $\geq 10\%$
    - Eosinophils absolute  $\geq 0.5\text{G/L}$
    - Neutrophils absolute  $< 1.5\text{G/L}$
    - Platelets  $\leq 100\text{G/L}$
    - ALT  $\geq 2\text{x ULN}$
    - AST  $\geq 2\text{x ULN}$
- Any indication of withdrawal symptoms using the Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B; Busto et al, 1989)

- Changes in suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS)

## 5 STUDY DESIGN

### 5.1 Study description

EP0069 is a Phase 2A, double-blind, randomized, placebo-controlled, multicenter study that will test the potential efficacy, safety/tolerability, and PK profile of UCB0942 in adult subjects with highly drug-resistant focal epilepsy. UCB0942 400mg bid will be administered as add-on to each subject's concomitant AED regimen.

Screening assessments will be conducted after subjects have understood the risks and potential benefits of the study and signed the written Informed Consent form (ICF). Only subjects who fulfill all eligibility criteria will be enrolled.

This study consists of:

- A 4-week prescreening Historical Baseline Period for study eligibility purposes
- A Screening Visit followed by a 2- to 3-week postscreening Prospective Outpatient Baseline Period (Day BL1 to Day BL14-21)
- A 3-week Inpatient Period, which consists of:
  - An Inpatient Titration Week (Day T1 to Day T7)
  - An Inpatient Maintenance-Dose Week (Day MD1 to Day MD7)
  - An Inpatient Transition-to-Outpatient Week (Day TTO1 to Day TTO7)
- An open-label Outpatient Maintenance Period of 8 weeks (Day OP1 to Day OP57)
- A Tapering Period of 2 weeks (Day TOO1 to Day TOO14)
- A Safety Follow-Up Period of 4 weeks (Day SFU1 to Day SFU28)
- An echocardiogram during dosing and after the last dose (the SFU7 echocardiogram). The echocardiogram will be repeated at 6 months ( $\pm 1$  month) after the last dose in the following subjects:
  - Subjects who complete this study but do not enter the OLE study
  - Subjects who withdraw from the Outpatient Period
  - Subjects who withdraw from the Inpatient Period and have an abnormal SFU7 echocardiogram

UCB0942 doses for placebo subjects will be titrated to UCB0942 400mg bid during the Inpatient Transition-to-Outpatient Week (Day TTO1 to Day TTO7). After the Inpatient Period, all subjects will continue in an open-label Outpatient Maintenance Period and a final Tapering Period of 2 weeks (Day TOO1 to Day TOO14). Doses for subjects continuing in the OLE study will not be tapered but will follow the schedule of safety and efficacy assessments as outlined in the OLE study protocol. Safety follow up will consist of 2 required visits, 1 and 4 weeks after the last dose of IMP (Day SFU7 and Day SFU28), and 1 optional visit 2 weeks after the last dose of IMP (Day SFU14). For details of the study assessments, refer to [Table 5-4](#). For a general presentation of the study design refer to [Figure 5-1](#).

#### Dosing in the Inpatient Period

*Titration Week (first week of the Inpatient Period)*



The objective of the Titration Week is to achieve the maximum UCB0942 dose of 400mg bid in as many of the subjects randomized to UCB0942 as possible while minimizing tolerability issues. During the Titration Week the dose for subjects randomized to UCB0942 will be titrated to UCB0942 400mg bid following the schedule in Table 5–1. The UCB0942 dose will be titrated to 400mg bid in a double-blinded fashion (ie, it will also appear that subjects randomized to placebo are being titrated). If, in the opinion of the Investigator, the Subject will be unable to titrate to the maximum dose of IMP due to intolerance of a lower dose, the Investigator should discuss this immediately with the Sponsor Study Physician, unless the subject's condition warrants immediate unblinding, and time does not allow discussion with the Sponsor. Unblinding may be required depending on the plan agreed upon by the Investigator and Sponsor Study Physician before dose tapering to UCB0942 200mg bid or 100mg bid. If unblinding reveals that the Subject is randomized to placebo, then further dosing with IMP will cease until the Transition-to-Outpatient Week (third week of the Inpatient Period), at which time, the Subject will titrate UCB0942 according to Table 5–1. All other assessments will continue as planned.

**Table 5–1: Dose titration to UCB0942 400mg bid**

	Day T1 <sup>a</sup>	Day T2	Day T3	Day T4	Day T5	Day T6	Day T7	Day MD1
AM	0	100mg	100mg	200mg	200mg	300mg	300mg	400mg
PM	100mg	100mg	200mg	200mg	300mg	300mg	400mg	400mg

AM=morning dose; PM=evening dose

<sup>a</sup> In placebo-arm subjects the same schedule is used from Day T1 to T7.

*Maintenance-Dose Week (second week of the Inpatient Period)*

If a subject is not tolerating the maximum dose of IMP well during the Maintenance-Dose Week such that the Investigator believes a dose reduction is necessary, then the Investigator should contact the Sponsor Study Physician to discuss the situation and agree upon a course of action. If a dose reduction is agreed, unblinding will be required. If the subject is randomized to UCB0942, the dose can be tapered from UCB0942 400mg bid to UCB0942 200mg bid. The taper from UCB0942 400mg bid to UCB0942 200mg bid will occur over 3 days (see Table 5–2). Dose tapering to UCB0942 100mg bid may also be permitted after discussion with the Sponsor's Study Physician. If it is revealed that the Subject is randomized to placebo, then further dosing with IMP will cease until the Transition-to-Outpatient Week (third week of the Inpatient Period), at which time, the Subject will titrate UCB0942 according to Table 5–1. All other assessments will continue as planned.

**Table 5–2: Taper from UCB0942 400mg bid to UCB0942 200mg bid**

	Taper Day 1	Taper Day 2	Taper Day 3	Taper Day 4 onwards
AM	300mg	300mg	200mg	200mg
PM	400mg	300mg	300mg	200mg

AM=morning dose; PM=evening dose

*Transition-to-Outpatient Week (third week of the Inpatient Period)*

The objective of the Transition-to-Outpatient Week is to achieve the maximum UCB0942 dose of 400mg bid in as many of the subjects randomized to placebo (now switching to

UCB0942) as possible while minimizing tolerability issues. The UCB0942 dose will be titrated to 400mg bid in a double-blinded fashion (ie, it will also appear that subjects randomized to UCB0942 are being titrated) following the schedule in Table 5–1. If, in the opinion of the Investigator, the Subject will be unable to titrate to the maximum dose of IMP due to intolerance of a lower dose, the Investigator should discuss this with the Sponsor Study Physician. Unblinding may be required depending on the plan agreed upon by the Investigator and Sponsor Study Physician.

#### Dosing in the Outpatient Maintenance Period and Tapering Period

During the Outpatient Maintenance Period, Subjects will continue to administer UCB0942 at the final Inpatient Period dose. Multiple adjustments (tapering or increase) of the dose are allowed during the Outpatient Maintenance Period (minimum 100mg bid and maximum 400mg bid); however, any change of dose in the Outpatient Maintenance Period should first be discussed with the Sponsor Study Physician.

At the end of the Outpatient Maintenance Period, or at the time a subject is withdrawn from the study, UCB0942 will be tapered following the schedule in Table 5–3. If the subject is not taking a dose of UCB0942 other than 400mg bid, then the Investigator should contact the Sponsor Study Physician to discuss the appropriate tapering schedule.

**Table 5–3: Dose taper from UCB0942 400mg bid**

Day	TOO1 to TOO4	TOO5 to TOO8	TOO9 to TOO12	TOO13 and TOO14
AM	300mg	200mg	100mg	
PM	300mg	200mg	100mg	100mg

AM=morning; PM=evening dose

In order to provide an ongoing assessment of the safety of subjects as the study progresses, a Safety Review Group (SRG) comprising appropriate Sponsor study team members and the Investigator(s) at each site will meet regularly to review appropriate safety data (see Section 11.1.9).

#### **5.1.1 Study duration per subject**

The total duration of the study after Screening is 20 weeks for each subject, including the Prospective Outpatient Baseline Period (2 to 3 weeks), the Inpatient Period (3 weeks), the Outpatient Period (8 weeks of treatment and 2 weeks of taper), and a SFU Period (4 weeks). In addition, there is an echocardiography visit at 6 months after the last dose. The total duration of exposure to UCB0942 during this study is 13 weeks.

The end of the study is defined as the date of the last visit of the last subject in the study.

#### **5.1.2 Planned number of subjects and sites**

Subjects with highly drug-resistant focal epilepsy will be enrolled at [REDACTED] sites in order to provide 46 evaluable subjects, ie, 46 subjects who complete the Inpatient Period. Subjects who drop out before Visit 6 (eg, during the Inpatient Period) for reasons other than safety or tolerability will be replaced. First subject, first visit is planned for Q2 2015.

#### **5.1.3 Anticipated regions and countries**

The study is planned to be performed in The [REDACTED]

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## 5.2 Schedule of study assessments

The schedule of study assessments is presented in [Table 5-4](#), and a detailed schedule of assessments for the Inpatient Period is presented in [Table 5-5](#).

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**Table 5-4: Schedule of study assessments**

Assessments	Baseline Period		Inpatient Period			Outpatient Period														
Period	Screening <sup>a</sup> / Baseline		Titration	Maintenance	Transition to Outpatient	Outpatient Maintenance Period										Taper/Safety Follow-Up Period				
Duration	1 day	2 weeks <sup>b</sup>	1 week	1 week	1 week	8 weeks										Up to 2 weeks		4 weeks		
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20
Study days	-1	BL1 to BL14/21	T1 to T7	MD1 to MD7	TTO1 to TTO7	OP 3	OP 5	OP 8	OP 15	OP 22	OP 29	OP 36	OP 43	OP 50	OP 57 <sup>c</sup>	TOO 7	TOO 14	SFU 7	SFU 14 <sup>d</sup>	SFU 28
						(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)
Written informed consent	X																			
Demographic data	X																			
Habits and lifestyle	X		X																	
General medical/medication/procedures history	X		X																	
Review historic seizure count	X																			
Verification of inclusion/exclusion criteria	X		X																	
Admission to clinic			X																	
Discharge from clinic					X <sup>e</sup>															
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination <sup>f</sup>	X		X	X	X					X					X		X	X	X	X

**Table 5-4: Schedule of study assessments**

Assessments	Baseline Period		Inpatient Period			Outpatient Period																		
Period	Screening <sup>a</sup> / Baseline		Titration	Maintenance	Transition to Outpatient	Outpatient Maintenance Period															Taper/Safety Follow-Up Period			
Duration	1 day	2 weeks <sup>b</sup>	1 week	1 week	1 week	8 weeks															Up to 2 weeks		4 weeks	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20				
Study days	-1	BL1 to BL14/21	T1 to T7	MD1 to MD7	TTO1 to TTO7	OP 3 (±2)	OP 5 (±2)	OP 8 (±2)	OP 15 (±2)	OP 22 (±2)	OP 29 (±2)	OP 36 (±2)	OP 43 (±2)	OP 50 (±2)	OP 57 <sup>c</sup> (±2)	TOO 7 (±2)	TOO 14 (±1)	SFU 7 (±1)	SFU 14 <sup>d</sup> (±2)	SFU 28 (±2)				
Neurological examination <sup>f</sup>	X		X	X	X					X					X		X	X	X	X				
Psychiatric and cognitive assessments <sup>g</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
CIWA-B <sup>h</sup>					X											X	X	X	X	X				
Vital signs (BP, pulse, and respiratory rate) <sup>i</sup>	X		X	X	X			X		X		X			X		X	X	X	X				
Body weight and height <sup>l</sup>	X		X		X					X					X					X				
12-lead ECG <sup>j</sup>	X		X	X	X					X					X		X			X				
Echocardiogram <sup>k</sup>	X									X								X						
Clinical laboratory <sup>l</sup>	X			X	X			X		X					X			X		X				
Video or video-EEG monitoring <sup>m</sup>			X	X	X																			
Pregnancy test <sup>n</sup>	X		X					X				X			X			X		X				

**Table 5-4: Schedule of study assessments**

Assessments		Baseline Period		Inpatient Period		Outpatient Period														
Period	Screening <sup>a</sup> / Baseline		Titration	Maintenance	Transition to Outpatient	Outpatient Maintenance Period										Taper/Safety Follow-Up Period				
Duration	1 day	2 weeks <sup>b</sup>	1 week	1 week	1 week	8 weeks										Up to 2 weeks		4 weeks		
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20
Study days	-1	BL1 to BL14/21	T1 to T7	MD1 to MD7	TTO1 to TTO7	OP 3	OP 5	OP 8	OP 15	OP 22	OP 29	OP 36	OP 43	OP 50	OP 57 <sup>c</sup>	TOO 7	TOO 14	SFU 7	SFU 14 <sup>d</sup>	SFU 28
Serology <sup>o</sup>	X					(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)
Screening for drug and alcohol use <sup>p</sup>	X		X						X						X					
Randomization <sup>q</sup>			X																	
Administration of IMP			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Sample for UCB0942, <div></div> plasma concentrations				X <sup>r</sup>		X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>					
Sample for DNA			X																	
Sample for mRNA/lipidomics/proteomics			X	X																
SSQ (Baseline version)			X	X	X					X					X		X	X		X
QOLIE-31-p <sup>t</sup>			X							X		X			X		X			

**Table 5-4: Schedule of study assessments**

Assessments	Baseline Period		Inpatient Period			Outpatient Period																			
Period	Screening <sup>a</sup> / Baseline		Titration	Maintenance	Transition to Outpatient	Outpatient Maintenance Period															Taper/Safety Follow-Up Period				
Duration	1 day	2 weeks <sup>b</sup>	1 week	1 week	1 week	8 weeks															Up to 2 weeks			4 weeks	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20					
Study days	-1	BL1 to BL14/21	T1 to T7	MD1 to MD7	TTO1 to TTO7	OP 3 (±2)	OP 5 (±2)	OP 8 (±2)	OP 15 (±2)	OP 22 (±2)	OP 29 (±2)	OP 36 (±2)	OP 43 (±2)	OP 50 (±2)	OP 57 <sup>c</sup> (±2)	TOO 7 (±2)	TOO 14 (±1)	SFU 7 (±1)	SFU 14 <sup>d</sup> (±2)	SFU 28 (±2)					
C-SSRS (Screening/ Baseline version)	X									X															
C-SSRS (Since last visit)			X	X	X					X					X			X		X					
Dispense IMP <sup>u</sup>			X	X	X				X		X		X		X										
IMP return <sup>v</sup>									X		X		X		X		X								
Dispense/return diary card	X	X <sup>w</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Diary Addendum <sup>x</sup>			X												1										
Concomitant medications/ procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
AED archive sample			X		X												X								
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					

**Table 5-4: Schedule of study assessments**

Assessments	Baseline Period		Inpatient Period			Outpatient Period															
Period	Screening <sup>a</sup> / Baseline		Titration	Maintenance	Transition to Outpatient	Outpatient Maintenance Period										Taper/Safety Follow-Up Period					
Duration	1 day	2 weeks <sup>b</sup>	1 week	1 week	1 week	8 weeks										Up to 2 weeks			4 weeks		
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	
Study days	-1	BL1 to BL14/21	T1 to T7	MD1 to MD7	TTO1 to TTO7	OP 3	OP 5	OP 8	OP 15	OP 22	OP 29	OP 36	OP 43	OP 50	OP 57 <sup>c</sup>	TOO 7	TOO 14	SFU 7	SFU 14 <sup>d</sup>	SFU 28	
						(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	

AE=adverse event; AED=antiepileptic drug; BL=Baseline; BP=blood pressure; BPRS=Brief Psychiatric Rating Scale; CIWA-B=Clinical Institute Withdrawal Assessment-Benzodiazepines; C-SSRS=Columbia-Suicide Severity Rating Scale; DBP=diastolic blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EEG=electroencephalogram; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C antibody; HIV-1/2Ab=human immunodeficiency virus-1/2 antibody; IMP=investigational medicinal product; IRT=interactive response technology; MD=Maintenance Dose; MINI=Mini International Neuropsychiatric Interview; MMSE=mini-mental state examination; mRNA=messenger ribonucleic acid; OLE=open-label extension; OP=Outpatient; PR=pulse rate; QOLIE-31-P=Quality of Life Inventory in Epilepsy-31-P; SBP=systolic blood pressure; SFU=Safety Follow-Up Visit; SSQ=Seizure Severity Questionnaire; T=Titration; TOO=Taper of Outpatient; TTO=Transition to Outpatient

<sup>a</sup> If a subject fails screening, a rescreening is allowed if deemed appropriate by the Investigator.

<sup>b</sup> Baseline Period of at least 2 weeks and no more than 3 weeks.

<sup>c</sup> Day OP57 is the same day as Day TOO1.

<sup>d</sup> SFU14 is optional, only if deemed necessary by the Investigator. Additional assessments can be added if necessary.

<sup>e</sup> On Day TTO7 after completing all assessments, subjects will be discharged.

<sup>f</sup> Physical examination (complete) and neurological examination at Screening and on Days MD1, TTO7, OP22, OP57, TOO14, SFU7, SFU14 (if deemed necessary by the Investigator), and SFU28. Physical examination (focused, or as per center policy) and neurological examination on Day T1.

<sup>g</sup> MINI at Screening; BPRS and MMSE at every visit. During the first week after discharge psychiatric symptoms will be assessed during each visit, using the BPRS and MMSE, and by phone, using the BPRS only, on the other days.

<sup>h</sup> CIWA-B will be performed before the evening dose on the last day before discharge from the inpatient unit.

<sup>i</sup> Vital signs include PR, respiratory rate, SBP, and DBP. In addition, at Day T1, MD7, and TTO7 body temperature should be measured; on Day T1 this should be prior to first administration of UCB0942. Obtain vital signs and a 12-lead ECG once in the morning, unless otherwise noted.

<sup>j</sup> Height at Screening only.

<sup>k</sup> In addition to the echocardiogram during dosing and after the last dose (SFU7), the echocardiogram will be repeated at 6 months (±1 month) after the last dose in the following subjects: 1) Subjects who complete this study but do not enter the OLE study, 2) Subjects who withdraw from the Outpatient Period, and 3)

Subjects who withdraw from the Inpatient Period and have an abnormal SFU7 echocardiogram. Please note that the during dosing time point of Day OP22 for the echocardiogram has a time window of  $\pm 1$  week instead of  $\pm 2$  days and the Day SFU7 echocardiogram has a time window of  $\pm 1$  week instead of  $\pm 1$  day.

<sup>l</sup> Clinical chemistry, hematology, and urinalysis.

<sup>m</sup> At the discretion of the Investigator, sites may or may not perform video or video-EEG monitoring during parts of the Inpatient Period or during the whole Inpatient Period.

<sup>n</sup> Urine or serum pregnancy test.

<sup>o</sup> Serology to include HIV-1/2Ab, HBsAg, and HCV-Ab.

<sup>p</sup> The drug screen will include amphetamines, benzodiazepines, barbiturates, cocaine, cannabinoids, methadone, opiates, and alcohol. Use of AED from one of the classes mentioned will be allowed if allowed by inclusion and exclusion criteria.

<sup>q</sup> Randomization on Day T1 before first IMP administration using IRT.

<sup>r</sup> Obtain blood samples for measurement of plasma concentration of UCB0942 and metabolites on Day MD1 and MD7, at the following times: predose (within 5min of dosing), then at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h postdose. Time windows for postdose samples are as follows:  $\pm 5$ min for the 0.5h, 1h, 1.5h, 2h, 3h, and 4h samples;  $\pm 10$ min for the 6h, 8h, and 12h samples. The 12h sample must be obtained prior to the pm dose.

<sup>s</sup> Obtain blood samples for measurement of trough levels of UCB0942 and metabolites just prior to the morning dose of UCB0942. If a predose sample is not possible prior to the morning dose a sample can be taken just prior to the evening dose of UCB0942. If no sample can be taken just prior to dosing, a postdose sample will be taken and the actual dosing and sampling times will be recorded.

<sup>t</sup> The QOLIE-31-P will be completed by all subjects prior to any other study procedures at the visit. At Day T1, QOLIE-31-P will be assessed in the morning before randomization.

<sup>u</sup> For the Outpatient Period, medication will be dispensed on Days TTO7, OP15, OP29, OP43, and OP57.

<sup>v</sup> Medication should be presented at each visit for check on compliance.

<sup>w</sup> During the Baseline Period the subjects should be called at least once to check on the completion of the diary card.

<sup>x</sup> The subject will be instructed to leave any questions blank that he/she does not feel comfortable answering.

<sup>y</sup> Collect at Day OP57 or at Early Withdrawal.

**Table 5-5: Schedule of study assessments, Inpatient Period**

Period	Titration							Maintenance							Transition to Outpatient						
	Visit 3							Visit 4							Visit 5						
	T1	T2	T3	T4	T5	T6	T7	MD1	MD2	MD3	MD4	MD5	MD6	MD7	TTO1	TTO2	TTO3	TTO4	TTO5	TTO6	TTO7
Study days																					
Admission to clinic <sup>a</sup>	X																				
Discharge from clinic																					X <sup>b</sup>
Habits and lifestyle	X																				
General Medical/Medication/ procedures history	X																				
Verification of inclusion/ exclusion criteria	X																				
Withdrawal criteria	X	X	X	X	X	X	X	X	X	X					X	X	X	X	X	X	X
Physical/Neurological examination (complete)	X <sup>c</sup>							X													X
Psychiatric assessment (BPRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive assessment (MMSE)	X			X			X			X				X				X			X
CIWA-B																				X <sup>d</sup>	
Vital signs (BP, pulse, and respiratory rate) <sup>e</sup>	X		X	X	X	X	X			X				X				X			X
Body temperature <sup>f</sup>	X													X							X
Body weight	X																				X
12-lead ECG <sup>e</sup>	X			X				X		X				X							X
Clinical laboratory <sup>g</sup>								X						X							X
Video or video-EEG monitoring <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test <sup>i</sup>	X																				

**Table 5–5: Schedule of study assessments, Inpatient Period**

Period	Titration							Maintenance							Transition to Outpatient						
	Visit 3							Visit 4							Visit 5						
	T1	T2	T3	T4	T5	T6	T7	MD1	MD2	MD3	MD4	MD5	MD6	MD7	TT01	TT02	TT03	TT04	TT05	TT06	TT07
Study days																					
Screening for drugs and alcohol	X																				
Randomization <sup>j</sup>	X																				
Administration of IMP <sup>k</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample for UCB0942, [REDACTED] plasma concentrations								X						X							
Sample for DNA	X																				
Sample for mRNA	X													X							
Sample for lipidomics	X													X							
Sample for proteomics	X													X							
SSQ (Baseline version) <sup>m</sup>	X							X						X							X
QOLIE-31-P <sup>m</sup>	X																				
C-SSRS (since last visit)	X							X						X							X
Diary card completion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IMP <sup>n</sup>	X							X							X						X
Dispense diary card <sup>n</sup>	X							X							X						X
Diary Addendum <sup>o</sup>	X																				
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AED archival sample	X																				X
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X



**Table 5-5: Schedule of study assessments, Inpatient Period**

Period	Titration							Maintenance							Transition to Outpatient						
Visit	Visit 3							Visit 4							Visit 5						
Study days	T1	T2	T3	T4	T5	T6	T7	MD1	MD2	MD3	MD4	MD5	MD6	MD7	TTO1	TTO2	TTO3	TTO4	TTO5	TTO6	TTO7

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BPRS=Brief Psychiatric Rating Scale; CIWA-B=Clinical Institute Withdrawal Assessment-Benzodiazepines; C-SSRS=Columbia-Suicide Severity Rating Scale; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EEG=electroencephalogram; IMP=investigational medicinal product; IRT=interactive response technology; MD=Maintenance Dose; MMSE=mini-mental state examination; mRNA=messenger ribonucleic acid; QOLIE-31-P=Quality of Life Inventory in Epilepsy-31-P; SSQ=Seizure Severity Questionnaire; T=Titration; TTO=Transition to Outpatient

<sup>a</sup> Admission in the morning of Day T1.

<sup>b</sup> Discharge after completion of all assessments on Day TTO7; pm dose is first outpatient dose.

<sup>c</sup> Physical examination can be focused on Day T1 if center procedures allow.

<sup>d</sup> CIWA-B will be performed before the evening dose on the last day before discharge from the inpatient unit.

<sup>e</sup> Obtain vital signs and a 12-lead ECG once in the morning, unless otherwise noted.

<sup>f</sup> Body temperature should be measured before the first dose of UCB0942 on Day T1.

<sup>g</sup> Clinical chemistry, hematology, and urinalysis.

<sup>h</sup> At the discretion of the Investigator, sites may or may not perform video or video-EEG monitoring during parts of the Inpatient Period or during the whole Inpatient Period.

<sup>i</sup> Urine or serum pregnancy test, female subject only.

<sup>j</sup> Randomization after completion of all assessments on Day T1 using IRT.

<sup>k</sup> First administration after randomization in the evening of Day T1 followed by bid dosing.

<sup>l</sup> Obtain blood samples for measurement of plasma concentration of UCB0942 and metabolites on Day MD1 and MD7, at the following times: predose (within 5min of dosing), then at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h postdose. Time windows for postdose samples are as follows:  $\pm 5$ min for the 0.5h, 1h, 1.5h, 2h, 3h, and 4h samples;  $\pm 10$ min for the 6h, 8h, and 12h samples. The 12h sample must be obtained prior to the pm dose.

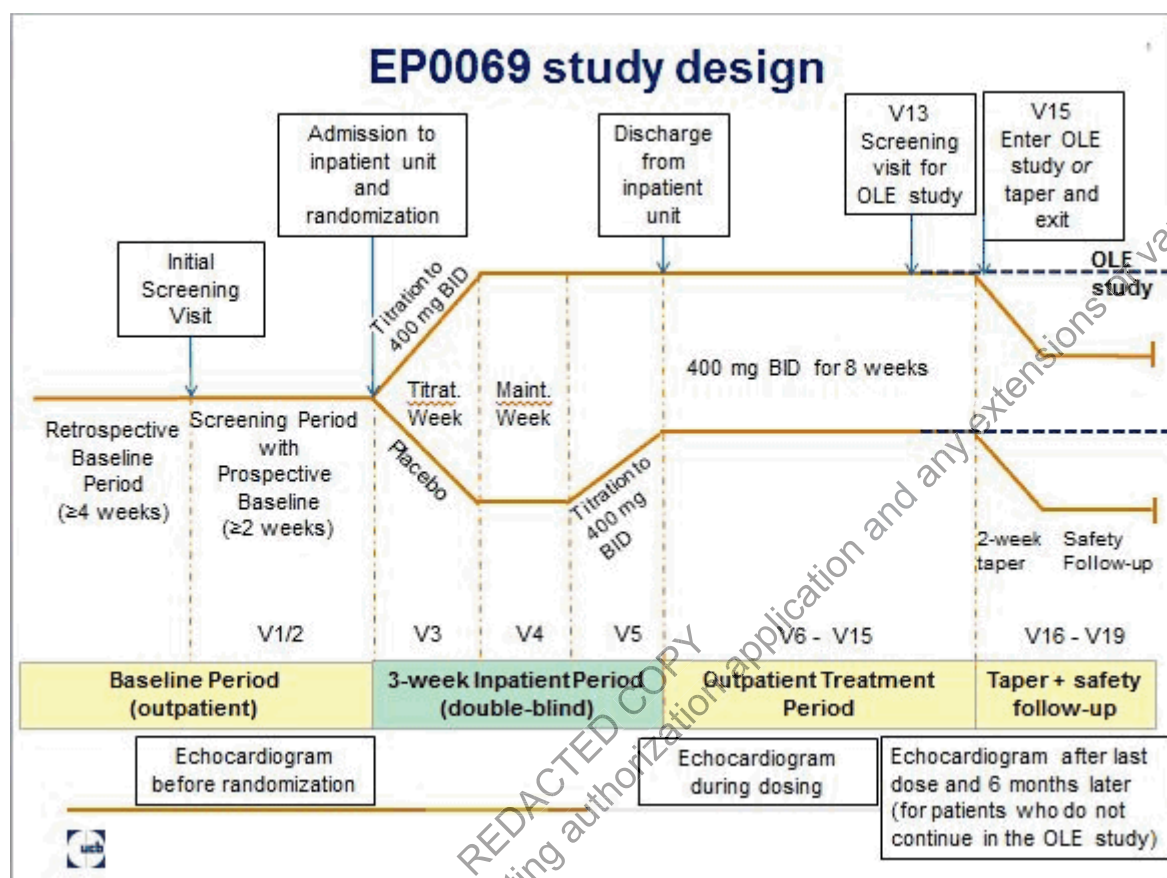
<sup>m</sup> The QOLIE-31-P and SSQ (Baseline version) will be completed by all subjects prior to any other study procedures at the visit.

<sup>n</sup> For the Outpatient Period, after completion of all assessments on Day TTO7.

<sup>o</sup> The subject will be instructed to leave any questions blank that he/she does not feel comfortable answering.

### 5.3 Schematic diagram

Figure 5–1: Study design



### 5.4 Rationale for study design and selection of dose

This multicenter, double-blind, randomized, placebo-controlled, parallel-group study will assess the safety and efficacy of UCB0942 in the adjunctive treatment of seizures with or without secondary generalization in adult subjects with highly drug-resistant focal epilepsy, for the first time. The study will have an Inpatient Period to minimize the psychiatric risk to subjects during the titration. The Outpatient Maintenance Period is necessary to ensure that any efficacy observed is maintained and that subjects do not develop tolerance to UCB0942.

The dose used in this study (UCB0942 400mg bid) was chosen because it is the maximum tolerated dose (MTD) in Phase 1 studies. This dose is expected to:

1. achieve exposures similar to those that show unprecedented efficacy in the rat amygdala kindling model of drug-resistant focal epilepsy,
2. achieve full and constant SV2 occupancy based on modeling predictions, and
3. achieve 10-15% occupancy of the cBZR site on the GABA-A receptor.

Based on previous experience in Phase 1, a dose titration over 1 week was chosen to minimize the occurrence of AEs. The titration will be performed during the Inpatient Period in all subjects (Section 8.2.1). If a subject does not tolerate UCB0942 400mg bid during the Maintenance-Dose Week or later, taper to UCB0942 200mg bid can be started by the Investigator.

The SRG will monitor the effectiveness of these strategies in controlling AEs on an ongoing basis, as detailed in Section 11.1.9.

## 6 SELECTION AND WITHDRAWAL OF SUBJECTS

### 6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. Subject is an adult (18 years of age or more).
2. Subject is able to understand the study and the ICF as assessed by the Investigator. Subjects with known mental retardation (defined as IQ below 70) are not eligible to participate.
3. A written ICF approved by the or Independent Ethics Committee (IEC) is signed and dated by the subject, after the Investigator assesses whether the subject is able to understand the potential risks and benefits of participating in the study. A separate ICF should be signed and dated by the subject to allow for the optional DNA, mRNA, and lipidomics/proteomics/additional blood biomarker samples.
4. Subject and/or caregiver is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and the medication intake scheme as instructed according to the judgment of the Investigator.
5. Subject is of normal weight as determined by a body mass index (BMI) between 16.0 and 40.0kg/m<sup>2</sup> (exclusive) and with a body weight of at least 50kg (males) or 45kg (females).
6. Subject fulfills ILAE (1989) criteria for focal epilepsy:
  - clinical semiology should be described and fulfill criteria for focal seizures.
  - there will have been an electroencephalogram (EEG) reading compatible with focal epilepsy in the last 5 years.
  - the subject has no seizures that are not focal by the new ILAE criteria.
  - a brain MRI (magnetic resonance imaging) or head CT (computed tomography) to be performed before randomization, if no such scan was performed in the last 5 years, and a report is available. If a scan was performed within the last 5 years but the epilepsy has not been stable since the last scan, a new scan should be obtained.
7. Subject has failed to achieve seizure control with  $\geq 4$  appropriately chosen AED regimens of adequate dose and duration, including the current treatment, as documented in medical records and per Investigator assessment of patient report.
8. Subject is currently treated with a stable dose of at least 1 AED for the 4 weeks prior to the Screening Visit (Visit 1) and throughout the duration of the Treatment Period with or without additional concurrent vagus nerve stimulation (VNS) or other neurostimulation treatments. The VNS must have been in place for at least 12 months with constant settings for at least 3 months and the battery life of unit anticipated to extend for the duration of study prior to the Screening Visit and throughout the duration of the study.
9. During the 4 weeks prior to Screening (Historical Baseline Period), subject must report to have had an average of at least 4 spontaneous and observable focal seizures per week ("focal seizures" refers to partial-onset seizures of type IA1, IB, and IC, but does *not* include type IA2, IA3, or IA4 seizures), and cannot have had any seizure-free period longer than 3 days (based on Investigator assessment of subject report and seizure diaries

if available). The cut-off seizure frequency (4 seizures per week) and maximum seizure-free interval (3 days) must be maintained during the 2-week Prospective Outpatient Baseline Period.

10. Subject has clinical laboratory test results within the reference ranges of the laboratory or isolated test results that are outside the specified ranges and that are deemed as not clinically significant by the Investigator.
11. Subject has blood pressure and heart rate within normal range in the supine position after 5 minutes rest, or the subject has hypertension that is under partial control with a stable antihypertensive medication regimen but that the Investigator deems as clinically not significant.
12. Female subjects of nonchildbearing potential (premenarcheal, postmenopausal for at least 2 years, bilateral oophorectomy or tubal ligation, and complete hysterectomy) are eligible. Female subjects of childbearing potential are eligible if they use medically accepted contraceptive methods. Oral or depot contraceptive treatment with at least ethinylestradiol 30µg per intake used with an additional barrier contraception method, monogamous relationship with vasectomized or female partner, or double-barrier contraception are acceptable methods. The subject must understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understand the proper use of contraceptive methods, and undertake to inform the Investigator of any potential change in status. Abstinence will be considered as an acceptable method of contraception if the Investigator can document that the subject agrees to be compliant when it is in line with the preferred and usual lifestyle of the subject.
13. Male subjects confirm that during the study period and for a period of 3 months after the final dose, when having sexual intercourse with a woman of childbearing potential, he will use a barrier contraceptive (eg, condom) and that the respective partner will use an additional contraceptive method.

## 6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject has participated in another study of an investigational medication (or medical device) within the last 30 days or is currently participating in another study of an investigational medication (or a medical device).
2. Subject has either:
  - >1.5x upper limit of normal (ULN) of any of the following:
    - alanine aminotransferase (ALT)
    - aspartate aminotransferase (AST)
    - alkaline phosphatase (ALP)

**-OR-**

- >ULN total bilirubin ( $\geq 1.5 \times$ ULN total bilirubin if known Gilbert's syndrome).

If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

For randomized subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the Case Report form (CRF).

If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

3. Subject has a known hypersensitivity to any components of UCB0942 formulation or to similar drugs (LEV, BRV, or benzodiazepines), or a history of drug or other allergy that, in the opinion of the Investigator or UCB Study Physician, contraindicates her/his participation.
4. Subject has had significant blood loss or has donated or received 1 or more units (450mL) of blood within 30 days prior to UCB0942 administration, or has donated plasma or platelets within 14 days prior to UCB0942 administration for this study.
5. Subject tests positive for human immunodeficiency virus-1/2 antibody (HIV-1/2Ab), hepatitis B surface antigen (HBsAg), or hepatitis C antibody (HCV-Ab).
6. Subject has a medical condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject's safety or his/her ability to participate in this study.
7. Subject has a current or past psychiatric condition that, in the opinion of the Investigator, could compromise his/her safety or ability to participate in this study including a history of schizophrenia, schizoaffective disorder, bipolar disorder, or severe unipolar depression. The presence of potential psychiatric exclusion criteria will be determined based on screening with the BPRS plus the Mini International Neuropsychiatric Interview (MINI).
8. Subject has a history of status epilepticus or has been hospitalized for status epilepticus within the 6-month period prior to Screening Visit.
9. Subject has had EEGs showing a pattern not consistent with a diagnosis of focal epilepsy (eg, generalized spike-wave).
10. Subject only has seizures that are uncountable due to clustering.
11. Subject has had pseudoseizures, conversion disorder, or other nonepileptic ictal events that, in the opinion of the Investigator, could be confused with seizures.
12. Subject had epilepsy surgery <1 year or an epilepsy dietary therapy initiated < 3 months prior to Screening.
13. Subject has taken other (non-AED) prescription, nonprescription, dietary (eg, grapefruit or passion fruit), or herbal products that are potent inducers or inhibitors of the CYP3A4 pathway for 2 weeks (or 5 half-lives, whichever is longer) prior to the Baseline Visit.
14. Subject is currently treated with carbamazepine, phenytoin, primidone, or phenobarbital or any other drug known as a strong inducer of CYP3A4 liver enzymes.
15. Subject is taking tiagabine, felbamate, or vigabatrin.
16. Subject is taking benzodiazepines, zolpidem, zaleplon, or zopiclone >3 times per week for any indication.
17. Subject had intolerable or serious psychiatric side effects with a previous exposure to LEV or BRV.



18. Subject has past or present substance abuse/dependence that in the opinion of the Investigator could threaten the subject's safety within the study, affect the subject's ability to fully participate in the study, or confound study interpretation.
19. Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response (Yes) to either Question 4 or Question 5 of the C-SSRS at Screening.
20. Subject has a clinically significant abnormality on ECG that, in the opinion of the Investigator, increases the risks associated with participating in the study. In addition, any subject with any of the following findings will be excluded:
  - QT corrected for heart rate using Bazett's formula (QTcB) or QT corrected for heart rate using Fridericia's formula (QTcF) interval >450ms
  - Bundle branch blocks and other conduction abnormalities that are clinically significant according to the Investigator and/or with a PR interval  $\geq 220$ ms
  - Irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats
  - In the judgment of the Investigator, T-wave configurations are not of sufficient quality for assessing QT interval duration.
21. Subject has a history of unexplained syncope or a family history of sudden death due to long QT syndrome.
22. Subject has a clinically significant abnormality on echocardiography at Screening or a history of rheumatic heart disease or other known valvular abnormalities.
23. Subjects with a history of hypersensitivity reactions or autoimmune disease.
24. Female subject who is pregnant or breastfeeding.

### 6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subject may be withdrawn by the Investigator if s/he is noncompliant with the study procedures or medications in a way that, in the opinion of the Investigator, may affect the study or the safety of the subject, or a subject is unable to manage the completion of the diary, or demonstrates a questionable diary.

Subjects must be withdrawn from the study if any of the following events occur:

1. Subject develops a clinically relevant medical condition (or laboratory abnormality) that, in the opinion of the Investigator, compromises the subject's ability to participate or safety. Potential drug-induced liver injury IMP discontinuation criteria are described in Section 6.3.1. To monitor for hypersensitivity reactions, percent eosinophils >10% or absolute eosinophil count  $\geq 0.5$ G/L or absolute neutrophil count <1.5G/L or absolute platelet count  $\leq 100$ G/L, if in combination with fever, rash, lymphadenopathy, or other symptoms/signs suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, or arthritis) will lead to stopping the IMP.
2. UCB or a regulatory agency requests withdrawal of the subject.

3. Subject develops psychiatric/mood/behavioral signs or disturbances (see examples in list below) that are clinically concerning or that worsen over time. Tapering and discontinuation of UCB0942 would be performed in such subjects and they would be referred to a mental healthcare professional.
  - a) Auditory or visual hallucinations
  - b) Delusions/paranoia/grandeur
  - c) Disorganized thought process
  - d) Agitation/aggression/apathy
  - e) Dysphoria/depression/mood lability/euphoria
  - f) Disinhibition
  - g) Cognitive changes/significant memory impairment
  - h) Delirium
  - i) Aberrant motor behavior
4. Subject requires treatment with a medication that is not permitted (Section 7.8.2) and is not allowed after discussion with the UCB Study Physician.
5. Subject becomes pregnant.
6. Subject has active suicidal ideation without specific plan as indicated by a positive response (“Yes”) to Question 4 of the “Since Last Visit” version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and may be withdrawn from the study based upon the Investigator’s judgment of benefit/risk of continuing the subject in the study on study medication. If the Subject has active suicidal ideation with a plan as indicated by a positive response (“Yes”) to Question 5 of the “Since Last Visit” version of the C-SSRS, the subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
7. Subject has a prolongation or worsening of overall seizure duration, frequency, type, or pattern considered by the Investigator as persistent and serious enough to warrant discontinuation from the study.

In the case of withdrawal or discontinuation during the study or during the echocardiography follow-up period, the Investigator should attempt to obtain information on subjects. For subjects considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The electronic Case Report form (eCRF) must document the primary reason for withdrawal or discontinuation.

The Investigator should contact the UCB Study Physician whenever possible to discuss the withdrawal of a subject in advance. If this is not possible, the Investigator should contact the UCB study physician to inform him/her about the subject withdrawal as soon as possible after the withdrawal.

### 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST  $\geq 5 \times \text{ULN}$
  - ALT or AST  $\geq 3 \times \text{ULN}$  and coexisting total bilirubin  $\geq 2 \times \text{ULN}$

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST  $\geq 3 \times \text{ULN}$  who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie,  $>5\%$ ).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 11.6.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

- Subjects with ALT or AST  $\geq 3 \times \text{ULN}$  (and  $\geq 2 \times$  baseline) and  $< 5 \times \text{ULN}$ , total bilirubin  $< 2 \times \text{ULN}$ , and no eosinophilia (ie,  $\leq 5\%$ ), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 11.6.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The CRF must document the primary reason for IMP discontinuation.



## 7 STUDY TREATMENTS

### 7.1 Description of investigational medicinal products

The details of the active and placebo IMP are displayed in [Table 7–1](#).

**Table 7–1: Description of investigational medicinal product**

	UCB0942	Placebo for UCB0942
Dosage form	Tablets (white, film-coated), in 2 strengths: <ul style="list-style-type: none"><li>- 100mg</li><li>- 200mg</li></ul> 100mg and 200mg tablets have the same size and appearance	Tablets (white, film-coated): Provided in a size and appearance matching UCB0942.
Manufacturer	[REDACTED]	
Batch/lot number	Will be assigned according to GMP	
Expiry date	Will be assigned according to GMP	

GMP=Good Manufacturing Practice

Note: For the Inpatient Period, 1 kit per treatment period and per dose will be packaged. Each kit will contain blister packs, each covering 1 week of treatment. For the Outpatient Period, UCB0942 tablets will be provided in bottles, containing 37 tablets per bottle, either 200mg tablets for subjects on UCB0942 400mg bid or UCB0942 200mg bid, or 100mg tablets for subjects who reduce dose to UCB0942 100mg bid. The bottles containing 37 UCB0942 100mg tablets will be dispensed for the Taper Period.

### 7.2 Treatments to be administered

#### 7.2.1 Test study medication

UCB0942 will be supplied by UCB as 100mg and 200mg tablets that are identical in appearance.

#### 7.2.2 Reference product

The placebo will be provided as tablets that are identical in appearance to the tablets containing UCB0942.

### 7.3 Packaging

All study medication for the double-blind Inpatient Period will be provided in blister packs and administered in a double-blind manner. All subjects will be instructed to take tablets containing either UCB0942 or placebo twice per day, approximately 12 hours apart. The blister-packed treatment cards will each provide 7 days' treatment of active or placebo UCB0942. For the open-label Outpatient Maintenance Period, tablets will be provided in

bottles, with a 2-week supply (see [Table 5-4](#)). For the Taper Period, bottles of 100mg tablets will be dispensed for 1-2 weeks, depending on dose from which the taper starts.

## **7.4 Labeling**

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) and will include any locally required statements. If necessary, labels will be translated into the local language.

## **7.5 Handling and storage requirements**

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access.

Appropriate room temperature storage conditions must be demonstrated by completion of a temperature log in accordance with local requirements, including the capture of minimum and maximum temperatures reached over a time interval. Temperatures, including minimum and maximum recordings, should be documented daily on the log during the site's days of operation. The IMP is to be stored according to the instructions on the label.

In case an out-of-range temperature is noted, it must be immediately communicated to the Exploratory Project Manager (EPM) (or designee) before further use of the IMP.

The EPM (or designee) will transmit the out-of-range temperature (copy of the temperature log and duration of the out-of-range temperature, if available) to the Drug Supply Coordinator. Based on discussion with a UCB Quality Assurance representative, the Drug Supply Coordinator will then provide the EPM (or designee) with instructions for the site regarding use of the IMP.

The Investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

## **7.6 Drug accountability**

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB (or designee), preferably in their original package. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

## **7.7 Procedures for monitoring subject compliance**

At each visit after where new IMP is dispensed and at the end of the Taper Period (Days OP15, OP29, OP43, OP57, and TOO14), subjects must return all unused IMP and empty IMP containers. Subjects will be asked to document drug intake on the subject diary throughout the Treatment Period. Drug accountability must be done in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a subject is found to be persistently noncompliant (defined as less than 75% or more than 125% compliant with the dosage schedule), the Sponsor, in conjunction with the Investigator, will make a decision as to whether the subject should be withdrawn from the study.

Timely completion of the subject diary is essential for evaluation of safety and efficacy. A caregiver is allowed to help the subject with the completion of the subject diary. Subject diary completion will be evaluated at each visit.

## **7.8 Concomitant medications/treatments**

### **7.8.1 Permitted concomitant treatments (medications and therapies)**

The following concomitant medications are permitted during the study:

- All subjects should continue using their Baseline AED regimen throughout the Inpatient Treatment Period. Changes in AEDs during the Outpatient Maintenance Period should be discussed with the UCB Study Physician on an individual and case-by-case basis.
- Oxcarbazepine, eslicarbazepine.
- Benzodiazepines (as a rescue medication less than or equal to 3 doses within 7 days).
- Other medication, not mentioned as prohibited, that does not induce CYP3A4 and is approved by the UCB Study Physician.

### **7.8.2 Prohibited concomitant treatments (medications and therapies)**

The following concomitant medications are prohibited during the study (this is not a complete list of prohibited medications):

- Carbamazepine, phenytoin, phenobarbital, primidone, or other strong CYP3A4 inducers
- Benzodiazepines taken >3 times per week (see Section 7.8.1)
- Zolpidem, zaleplon, or zopiclone taken >3 times per week
- Tiagabine
- Felbamate
- Vigabatrin
- Non-AED CYP3A4 inducers/inhibitors (ie, prescription drugs, nonprescription drugs, dietary [eg, grapefruit or passion fruit], or herbal products)

### **7.8.3 Rescue medication**

Benzodiazepines can be used as rescue medication (less than or equal to 3 doses within 7 days).

## 7.9 Blinding

This is a study with a double-blind Inpatient Period and an open-label Outpatient Period. At the start of the Titration Period (Day T1) subjects will be randomized to UCB0942 400mg bid or placebo in a 1:1 ratio.

The randomization will be stratified for the following LEV prior/current use factor to ensure the balance across treatment groups (Placebo, UCB0942 400mg bid):

- use of LEV (3 levels):
  1. LEV prior and current use (concomitant use of LEV at study entry)
  2. LEV Prior Use Only=History of prior LEV use and must have discontinued 4 weeks prior to study entry
  3. LEV Naïve=No history of prior LEV use, and no use at study entry

### 7.9.1 Procedures for maintaining and breaking the treatment blind

#### 7.9.1.1 Maintenance of study treatment blind

All subject treatment details will be allocated and maintained by the interactive response technology (IRT). Details of the IRT system will be addressed in a separate randomization schedule specification document.

#### 7.9.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine which treatment arm and dose the subject has been allocated to by contacting the IRT. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

The EPM will be informed immediately via the IRT when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the Investigator must be recorded in the source documents and on the Study Termination eCRF page.

The SRG may also elect to break the blind for individual subjects as part of its review process, in order to better assess the significance and response to AEs of concern (see Section 11.1.9).

#### 7.9.1.3 Breaking the treatment blind for taper of dose during the study

When the Investigator and Sponsor Study Physician agree that a subject cannot titrate to the maximum dose or that a dose reduction is necessary during the Inpatient Period (See Section 5.1, the blind will have to be broken, following the procedure described in Section 7.9.1.2.

## 7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by the IRT vendor. The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of study drug, as appropriate, according to the visit schedule.

To enroll a subject (Visit 1), the Investigator or designee will contact the IRT and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at Screening that serves as the subject identifier throughout the study. The subject

number will be required in all communication between the Investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

To randomize a subject (Visit 3), the Investigator or designee will contact the IRT and provide brief details about the subject to be randomized. The IRT will automatically inform the Investigator or designee of the subject's randomization number. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study.

After completion of the Inpatient Maintenance Period, doses for subjects receiving placebo will be titrated to the Outpatient Maintenance Dose (Day TTO 1 to TTO7). To ensure continued blinding all subjects will remain in the clinic for this titration period.

## **8 STUDY PROCEDURES BY VISIT**

Details of the study assessments to be performed at specific time points prior to and after IMP administration are provided in [Table 5-4](#), and an outline of all assessments performed is provided in the sections below.

The total blood collection for the study will not exceed 500mL per subject.

### **8.1 Screening and Baseline Period**

#### **8.1.1 Screening (Visit 1, Day -1)**

- Written informed consent
- Complete medical, medication, and procedure history recording
- Concomitant and past AEDs
- Review of historic seizure count (ie, in the preceding 4 weeks)
- Review of inclusion/exclusion criteria
- Date of birth, sex, ethnicity, and race
- Habits and lifestyle
- Physical examination (complete)
- Neurological examination
- Psychiatric and cognitive assessments (MINI, BPRS, and MMSE)
- Vital signs (blood pressure [BP], pulse, and respiratory rate)
- Body weight and height
- 12-lead ECG
- Echocardiogram (this can be done on a different day but must be done before dosing with UCB0942)
- Clinical laboratory (clinical chemistry, hematology, and urinalysis)
- Urine or serum pregnancy test (female subjects only)
- Drug and alcohol screening
- Serology (HIV-1/2Ab, HBsAg, and HCV-Ab)
- C-SSRS (Screening/Baseline version)

- Diary card dispense

### **8.1.2 Baseline Period (Visit 2, Day BL1 to BL14-21)**

The Baseline Period (Day BL1 to BL14-21) will commence the day after the first day of Screening and will start no more than 3 weeks before entry into the clinic for the Inpatient Period.

During the Baseline Period a phone call will be made to the subject to verify completion of the diary card and to confirm the T1 admission day.

Screening assessments that cannot be completed on the first screening visit (eg, brain imaging with MRI or CT and echocardiogram) can be performed at any time during the Baseline Period but must be completed before the first dose of UCB0942.

If a subject fails screening, a rescreening is allowed if deemed appropriate by the Investigator.

## **8.2 Inpatient Period (3 weeks)**

Details of the study assessments to be performed at specific time points during the Inpatient Period are provided in [Table 5–5](#).

An outline of all assessments performed is provided in the sections below.

### **8.2.1 Titration Week (Visit 3, Day T1 to Day T7)**

At the discretion of the Investigator, sites may or may not perform video or video-EEG monitoring during parts of the Inpatient Period or during the whole Inpatient Period of the study, depending on the infrastructure of each site, to provide objective data on seizure type, severity, and duration, and on the duration of the postictal period as an exploratory outcome measure. The following assessments will be performed at admission to the clinic on Day T1 before administration of IMP:

- Return of diary cards and seizure count for the Prospective Outpatient Baseline Period to verify continued eligibility to participate in the study
- Dispense of new diary card
- Habits and lifestyle
- Concomitant medication/procedures
- Urine or serum pregnancy test (female subjects only)
- Drug and alcohol screening
- Review of inclusion/exclusion criteria
- Withdrawal criteria assessment
- Physical examination (focused)
- Neurological examination
- Psychiatric monitoring with BPRS
- Cognitive monitoring with MMSE
- Vital signs (BP, pulse, temperature, and respiratory rate)
- Body weight



- 12-lead ECG
- Blood sample for DNA
- Blood sample for mRNA
- Blood sample for lipidomics/proteomics/additional biomarkers
- Blood sample for AED (archival)
- SSQ (Baseline version)
- QOLIE-31-P
- Diary Addendum (T1)
- C-SSRS (since last visit)
- Concomitant AEDs
- Concomitant medication/procedures
- AEs
- Randomization (after all assessments have been done)

Subjects randomized to the active group will be titrated up to UCB0942 400mg bid over 1 week, as shown in [Table 5–1](#). Subjects randomized to placebo will do a dummy titration. After all admission assessments have been completed, all subjects will be given their first 100mg dose of IMP (or placebo) in the evening under medical supervision. During the double-blind part of the study, subjects in both arms will take the same number of tablets. All subjects will continue to record their seizures in subject diaries during the Titration Week.

During the Titration Week the following assessments will be performed as outlined in the schedule of assessments ([Table 5–5](#)):

- Return and dispense of diary card (Day T1)
- Video or video-EEG monitoring (optional)
- Withdrawal criteria assessment
- Psychiatric monitoring with BPRS
- Cognitive monitoring with MMSE (Days T4 and T7)
- Vital signs (BP, pulse, and respiratory rate; Days T3, T5, and T7)
- 12-lead ECG (Day T4)
- Administration of IMP and Baseline AED regimens
- Concomitant AEDs
- Concomitant medication/procedures
- AEs

### **8.2.2 Maintenance-Dose Week (Visit 4, Day MD1 to Day MD7)**

At the end of the Titration Week, subjects continue in the Maintenance-Dose Week, during which they will continue to record their seizures in subject diaries.



During this period the following assessments will be performed as outlined in the schedule of assessments (Table 5–5):

- Return and dispense of diary card
- Video or video-EEG monitoring (optional)
- Withdrawal criteria assessment
- Physical examination (complete, Day MD1)
- Neurological examination (Day MD1)
- Vital signs (BP, pulse, and respiratory rate; Days MD3 and MD7)
- Body temperature (Day MD7)
- 12-lead ECG (Days MD1, MD3, and MD7)
- Clinical laboratory (clinical chemistry, hematology, and urinalysis; Days MD1 and MD7)
- C-SSRS (since last visit; Days MD1 and MD7)
- Psychiatric monitoring with BPRS
- Cognitive monitoring with MMSE (Days MD3 and MD7)
- Administration of IMP and Baseline AED regimens
- On Day MD1 and MD7, blood samples for measurement of plasma concentration of UCB0942 and metabolites at the following times: predose (within 5min of the morning dose), then at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h postdose. All times relative to morning IMP administration time.
- Blood sample for mRNA (Day MD7)
- Blood sample for lipidomics/proteomics/additional biomarkers (Day MD7)
- Concomitant AEDs
- Concomitant medication/procedures
- AEs
- SSQ (Baseline version) for previous week on Day MD1 and MD7

### 8.2.3 Transition-to-Outpatient Week (Visit 5, Day TTO1 to Day TTO7)

After the end of the Maintenance-Dose Week, subjects will continue to take IMP if this is well tolerated (as determined by the Investigator and the subject). If a subject in the active arm is not tolerating UCB0942 400mg bid well during the Maintenance-Dose Week, the dose can be tapered to UCB0942 200mg bid during the Transition-to-Outpatient Week before discharge to the Outpatient Maintenance Period. In this case, the blind will be broken. The taper from UCB0942 400mg bid to UCB0942 200mg bid would occur over 3 days (see Table 5–2).

UCB0942 doses for subjects in the placebo arm will be titrated to UCB0942 400mg bid in the same way as the doses for subjects in the active arm were titrated during the Titration Week (Table 5–1). If UCB0942 is well tolerated during the titration, subjects in the placebo arm will be discharged on UCB0942 400mg bid and followed in the Outpatient Maintenance Period. If a subject in the placebo arm cannot tolerate the titration up to UCB0942 400mg

bid, the blind will be broken and the subjects will remain on a tolerable dose (ie, UCB0942 200mg bid) before starting the Outpatient Maintenance Period.

The entire Inpatient Period will be double-blind (except in cases in which the dose needs to be reduced or the taper cannot be completed, as described above); however, subjects and staff will know that at discharge all subjects are taking active compound. Therefore, the Outpatient Period is open-label.

During the Transition-to-Outpatient Week the following assessments will be performed as outlined in the schedule of assessments (Table 5–5):

- Return and dispense of diary card
- Video or video-EEG monitoring (optional)
- Withdrawal criteria assessment
- Physical examination (complete; Day TTO7)
- Neurological examination (Day TTO7)
- Vital signs (BP, pulse, and respiratory rate; Days TTO4 and TTO7)
- Body temperature (Day TTO7)
- Body weight (Day TTO7)
- 12-lead ECG (Day TTO7)
- Clinical laboratory (clinical chemistry, hematology, and urinalysis; Day TTO7)
- Administration of IMP and Baseline AED regimens
- Psychiatric monitoring with BPRS
- Cognitive monitoring with MMSE (Days TTO4 and TTO7)
- Withdrawal monitoring with CIWA-B (before evening dose on Day TTO6)
- SSQ (Baseline version) (Day TTO7)
- C-SSRS (since last visit; Day TTO7)
- Blood sample for AED (archival; Day TTO7)
- Concomitant AEDs
- Concomitant medication/procedures
- AEs

Upon release from the clinic subjects will receive IMP for 2 weeks and a diary card for the first week of the Outpatient Maintenance Period.

### **8.3 Outpatient Period (14 weeks)**

#### **8.3.1 Outpatient Maintenance Period (Visit 6 to Visit 15, Day OP1 to Day OP57)**

All subjects will take active UCB0942 during the Outpatient Maintenance Period; however, they will not know whether they were taking active or placebo during the Inpatient Period. If well tolerated, all subjects will continue to take UCB0942 400mg bid for 8 weeks during the Outpatient Maintenance Period. At any time during the Outpatient Maintenance Period, if a

subject does not tolerate UCB0942 400mg bid, the Investigator can decide to taper to UCB0942 200mg bid as shown in [Table 5–2](#). During the first week of the Outpatient Maintenance Period, all subjects will undergo psychiatric monitoring by phone on the days they do not visit the clinic (Days OP1, OP2, OP4, OP6, and OP7) and in person in the clinic on Days OP3, OP5, and OP8. Cognitive monitoring with MMSE will take place in the clinic on Days OP3, OP5, and OP8. This monitoring is necessary because the subjects initially randomized to placebo will be discharged directly after the titration to UCB0942 400mg bid and psychiatric AEs are most likely to occur in the first 2 weeks of UCB0942 administration.

During the Outpatient Maintenance Period subjects will visit the clinic on the following days ( $\pm 2$  days to allow for weekend interruptions):

Day OP3, OP5, OP8, OP15, OP22, OP29, OP36, OP43, OP50, and OP57.

When possible, outpatient clinic visit days will take place in the morning to allow dosing to take place in the clinic and collection of a predose blood sample for evaluation of trough PK levels at specific visits.

Dose tapering from UCB0942 400mg bid to UCB0942 200mg bid to increase tolerability may be implemented for each subject at any time during the 8 weeks of treatment in the Outpatient Maintenance Period at the discretion of the Investigator in conjunction with the wishes of the subject. Dose tapering to UCB0942 100mg bid may be permitted after discussion with the Sponsor's Study Physician.

During this period the following assessments will be performed according to the schedule of assessments ([Table 5-4](#)):

- Return and dispense of diary cards at each visit
- Return IMP (Days OP15, OP29, OP43, and OP57)
- Dispense IMP (Days OP15, OP29, OP43, and OP57)
- Administration of IMP
- Withdrawal criteria will be assessed at each visit
- Physical examination (complete; Days OP22 and OP57)
- Body weight (Days OP22 and OP57)
- Neurological examination (Days OP22 and OP57)
- Vital signs (BP, pulse, and respiratory rate; Days OP8, OP22, OP36, and OP57)
- 12-lead ECG (Days OP22 and OP57)
- Echocardiogram (Day OP22  $\pm 1$  week)
- Clinical laboratory (clinical chemistry, hematology, urinalysis; Days OP8, OP22, and OP57)
- Drug and alcohol screening (Days 22 and OP57)
- Urine or serum pregnancy test (females only; Days OP8, OP36, and OP57)
- Obtain blood samples for measurement of plasma concentration of UCB0942 and metabolites before morning dose (Days OP3, OP5, OP8, OP15, OP22, OP29, OP36, OP43, OP50, and OP57)

- Psychiatric monitoring with BPRS at the visits (Days OP3, OP5, OP8, OP15, OP22, OP29, OP36, OP43, OP50, and OP57) and by phone (Days OP1, OP2, OP4, OP6, and OP7)
- Cognitive monitoring with MMSE at the visits (Days OP3, OP5, OP8, OP15, OP22, OP29, OP36, OP43, OP50, and OP57)
- SSQ (Baseline version) (Days OP22 and OP57)
- QOLIE-31-P questionnaire (Days OP22, OP36, and OP57)
- Diary Addendum (OP57)
- C-SSRS (since last visit; Days OP22 and OP57)
- Concomitant AEDs recording
- Concomitant medication/procedures recording
- AEs recording
- Decision to continue in the OLE study (Day OP43)

### 8.3.2 Taper Period (Visit 15 to Visit 17, Day OP57 to TOO14)

All subjects who do not continue into the OLE study (see Section 8.6) will undergo a Taper and Safety Follow-Up Period to taper off study medication over a 2-week period (Table 5-3). Subjects will start their taper on Day OP57 (Visit 15) and will return for the Mid Taper Visit (Day TOO7) after 1 week and for the End of Taper Visit (Day TOO14) after 2 weeks. Changes to concomitant AED(s) are allowed during taper of UCB0942. Subjects can also start this taper earlier during the Outpatient Maintenance Period, if they decide to exit the study early.

During this period the following assessments will be performed as outlined in the schedule of assessments (Table 5-4):

- Return and dispense of diary cards at each visit
- Withdrawal criteria will be assessed at each visit
- Administration of IMP
- Physical examination (Day TOO14)
- Neurological examination (Day TOO14)
- Vital signs (BP, pulse, and respiratory rate) (Day TOO14)
- 12-lead ECG (Day TOO14)
- Return IMP (Day TOO14)
- SSQ (Baseline version) (Day TOO14)
- QOLIE-31-P questionnaire (Day TOO14)
- Psychiatric monitoring with BPRS (Days TOO7 and TOO14)
- Cognitive monitoring with MMSE (Days TOO7 and TOO14)
- Withdrawal monitoring with CIWA-B (Days TOO7 and TOO14)
- Concomitant AEDs

- AED archival sample (Day TOO14)
- Concomitant medication/procedures
- AEs

### **8.3.3 Safety Follow-Up (Visit 18 to 20, Day SFU7, SFU14, and SFU28)**

Two SFU visits are planned: the first SFU is planned 1 week after the end of the Taper Period (SFU7) and a final SFU 4 weeks after the end of the Taper Period (SFU28). During these visits the following assessments will be performed:

- Return of diary card (Day SFU7, SFU14 [optional], and SFU28), dispense of diary card (Day SFU7 and SFU14 [optional])
- Physical examination
- Neurological examination
- Vital signs (BP, pulse, and respiratory rate)
- Body weight (Day SFU28)
- 12-lead ECG (Day SFU28)
- Clinical laboratory (clinical chemistry, hematology, and urinalysis)
- Echocardiogram after last dose and 6 months later ( $\pm 1$  month). For subjects who withdraw during the Inpatient Period and for subjects who withdraw during the Outpatient Period, see Section 8.4 for echocardiogram requirements following withdrawal.
- Pregnancy test (urine or serum, females only)
- SSQ (Baseline version)
- C-SSRS (since last visit)
- Psychiatric monitoring with BPRS
- Cognitive monitoring with MMSE
- Withdrawal monitoring with CIWA-B
- Concomitant medication/procedures
- AEs

If deemed necessary by the Investigator 1 additional SFU visit can be planned one week after Day SFU7 (Day SFU14) containing those assessments deemed necessary by the Investigator.

### **8.3.4 Echocardiography follow up**

For subjects who complete this study but do not continue in the OLE study, it is mandatory that they have an echocardiogram at 6 months ( $\pm 1$  month) after the last dose of IMP (in addition to the echocardiogram at Screening, during dosing, and after the last dose).

## **8.4 Withdrawal Visit**

In case of early withdrawal of the subject for any reason, all efforts should be taken to have a safety follow-up visit as described in Section 8.3.3.

If a complete SFU is not feasible, at least the following assessments will be performed:

- Physical examination
- Neurological examination
- Vital signs (BP, pulse, and respiratory rate)
- Body weight
- 12-lead ECG
- Echocardiogram
  - Withdrawal during the Inpatient Period: The SFU7 echocardiogram should be performed. If there is no abnormality, the echocardiogram does not need to be repeated. If there is an abnormality, the echocardiogram should be repeated at 6 months ( $\pm 1$  month) after the last dose of IMP.
  - Withdrawal during the Outpatient Period: The SFU7 echocardiogram should be performed, and the echocardiogram should be repeated at 6 months ( $\pm 1$  month) after the last dose of IMP.
- Clinical laboratory (clinical chemistry, hematology, and urinalysis)
- Pregnancy test (urine or serum, females only)
- Diary Addendum
- C-SSRS
- Concomitant medication/procedures
- AEs

## 8.5 Unscheduled Visit

At any time, the subject may have an unscheduled clinic visit/phone call if the Investigator or the subject deems it necessary.

During an Unscheduled Visit the assessments will be performed as applicable as judged by the Investigator

## 8.6 Open-label extension study (EP0073)

Subjects who experience substantial benefit from UCB0942 with acceptable tolerability may have the option to continue taking UCB0942 during an OLE study. The decision to enter the OLE study must be made by the subject in consultation with the Investigator and/or the subject's caregiver. This decision must take into account the benefit experienced, the potential risks of long-term exposure to UCB0942, and the potential benefit and risks of other treatment options available. Subjects who enter the OLE study will have echocardiographic follow up as scheduled in the OLE study protocol and will therefore not participate in the echocardiographic follow up described in Section 8.3.4.

## 9 ASSESSMENT OF EFFICACY

The efficacy variables are described in detail in Section 4.1.

### 9.1 Seizure frequency

At the Screening Visit, seizure count will be based on Investigator assessment of subjects' reports during the 4 weeks prior to the Screening Visit, which will determine the subject's eligibility for the study. The minimum required historic seizure count during the 4 weeks



prior to Screening is 4 partial-onset seizures (IA1, IB, or IC according to the International Classification of Epileptic Seizures, 1981) per week on average with no seizure-free period longer than 3 days (based on Investigator assessment of subject report). During the study, subjects will keep diaries to record daily seizure activity from the Screening Visit until the end of study participation. Subjects should be reminded to bring their diaries with them to each clinic visit.

The written information will be discussed with the subjects at each visit in order to ensure completeness and accuracy. As a result of the discussion, the Investigator will assess the seizures according to the ILAE codes and record the seizure types and frequency in the eCRF; he/she will also confirm the presence of AEs if applicable.

Subjects should be educated to complete their diary entries after each seizure or at least once a day (eg, when taking evening tablets). A caregiver can assist in completing the diary if necessary. Substantial noncompliance with diary completion (seizure recording) may result in subject discontinuation from the study at any time by the Investigator or the Sponsor; see Section 6.3.

The following seizure information will be recorded in the diary:

- Seizure type
- Seizure frequency

### 9.1.1 Video monitoring

At the discretion of the Investigator, sites may or may not perform video or video-EEG monitoring during part of the Inpatient Period or during the whole Inpatient Period, depending on the infrastructure of each site, to allow exploratory analysis of seizure type, severity, and duration, and of the duration of the postictal period.

## 9.2 Seizure Severity Questionnaire

The SSQ (Cramer et al, 2002) is a review of various aspects of seizures. The person who has seizures may ask people who have observed the seizures (family, friends) to help answer some of the questions asking about events, but not about feelings. There are 10 questions in 3 sections asking about events before, during, and after typical seizures.

The subject should describe their most common type of seizure when answering the questions. If subjects are unsure about how to answer a question, they should give the best answer they can and write a comment or explanation on the side of the page.

The Baseline SSQ will be completed according to the tabular schedule of study procedures, Table 5-4. The Baseline version of the SSQ will be used for all visits during which the SSQ is to be completed. For this study the recall period will be set to 1 week rather than the original 4 weeks. At the very beginning of the visit, the SSQ will be provided to all subjects. The subject will be asked to complete the questionnaire on his/her own. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the SSQ will be covered in the Study Manual.

## 9.3 Quality of Life Inventory in Epilepsy-31-P

The QOLIE-31-P assesses subject functioning and health-related quality of life.

The QOLIE-31-P (Cramer et al, 2003) is an adaptation of the original QOLIE-31 instrument (Cramer et al, 1998) that includes 30 items grouped into 7 multi-item subscales (Seizure



Worry [5 items], Overall Quality of Life [2 items], Emotional Well-being [5 items], Energy/Fatigue [4 items], Cognitive Functioning [6 items], Medication Effects [3 items], and Daily Activities/Social Functioning [5 items]) and 1 health status item.

In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items assessing the degree of “distress” associated with the topic of each subscale (ie, distress items) and 1 item asking about the relative importance of each subscale topic (ie, prioritization item).

The QOLIE-31-P will be completed according to the tabular schedule of study procedures in Table 5-4. At the very beginning of the visit, the QOLIE-31-P will be provided to all subjects. The subject will be asked to complete the questionnaire on his/her own. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the QOLIE-31-P will be covered in the Study Manual.

## 9.4 Diary Addendum

A Diary Addendum will be completed according to the tabular schedule of study procedures in Table 5-4 as well as at the Withdrawal Visit, if applicable. The Diary Addendum will consist of a series of open-ended questions including the following:

- Why did you agree to take part in this study?
- What are your hopes for this new treatment?
- What are the biggest impacts of seizures on your life currently?
- What was your experience like during the study?
- Did participating in the study fulfill any of the hopes you had going into the study?
- How do you describe the impact of seizures on your life now? Has that changed since the beginning of the study?

Subjects will be instructed to leave any question blank that he/she does not feel comfortable answering.

## 10 ASSESSMENT OF PK AND EXPLORATORY VARIABLES

### 10.1 Pharmacokinetic parameters

The PK variables are described in detail in Section 4.2. Calculations of PK parameters will be made with Phoenix WinNonlin (version 6.2 or higher) using the actual sampling times and are described in Section 13.4.2. The linear trapezoidal method will be used to calculate the AUC parameters.

Detailed information on the collection, storage, preparation, and shipping of samples will be presented in a Laboratory Manual.

### 10.2 Exploratory parameters

Detailed information on the collection, storage, preparation, and shipping of samples for DNA, mRNA, lipidomics, and proteomics analysis will be presented in a Laboratory Manual.

Results for the exploratory parameters obtained from DNA, mRNA, lipidomics, and proteomics analysis will be described in a separate report.

### 10.3 Sampling procedures

Blood samples for PK and exploratory variables will be obtained at the scheduled time points presented in Table 5-4.

Times for PK samplings will be taken with respect to the time of the morning UCB0942 dose on the first and last day of the Maintenance-Dose Week, taken as Time 0=0h. Exact sampling times will be recorded in the eCRF.

Predose blood samples for levels of UCB0942 and its major metabolites will be obtained after ECGs and vital signs but prior to dosing of the study medication at Visit 4 and Visit 5.

Predose (trough) blood samples for levels of UCB0942 and its major metabolites will be obtained at Visits 6 to 15. The Investigator and the subject should make a realistic effort to plan the visits during the Outpatient Maintenance Period before the morning or the evening dose of UCB0942. If a predose blood sample is not feasible for a specific visit, a postdose blood sample should be collected and the actual times of the dosing and sampling recorded.

For the exploratory assessments, the processing of the blood samples will be described in the Laboratory Manual. One sample each will be collected for the mRNA, lipidomics, and proteomics assay.

For the AED archival samples, processing will be described in the Laboratory Manual.

Preprinted labels will be provided by the analytical laboratory of UCB. Laboratory kits will be provided by UCB or a delegate.

### 10.4 Bioanalytical methods

Plasma concentrations of UCB0942 and metabolites [REDACTED] will be determined using validated bioanalytical methods.

### 10.5 Pharmacokinetic/pharmacodynamic relationships

If appropriate, a population PK analysis will be performed, as described in Section 13.4.2.

If needed, exploratory exposure-response analysis will be performed to describe the relationship between the exposure to UCB0942 and the efficacy and/or safety variables.

## 11 ASSESSMENT OF SAFETY

### 11.1 Adverse events

#### 11.1.1 Definition of adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, ie, through the end of the Taper/Safety Follow-up Period, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the investigational product is being studied (ie, seizures) should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.

### **11.1.2 Procedures for reporting and recording adverse events**

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

“Did you notice anything unusual about your health (since your last visit)?”

In addition, the Investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

### **11.1.3 Description of adverse events**

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

### **11.1.4 Follow up of adverse events**

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

If an AE is ongoing at the end of the Taper/Safety Follow-up Period, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 30 days after the subject has discontinued his/her IMP.

Adverse events should not be recorded in the eCRF after the end of the Taper/Safety Follow-up Period.

### **11.1.5 Rule for repetition of an adverse event**

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of “worsening”
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

### **11.1.6 Pregnancy**

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's Drug Safety (DS) department by providing the completed Pregnancy Report and Outcome form (for contact details see SAE reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of the IMP or be tapered as instructed at the early discontinuation visit.
- A Safety Follow-Up Visit should be scheduled 1 week after the subject has discontinued her IMP.

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's DS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/contract research organization (CRO) contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's DS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's DS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes a SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

#### **11.1.7 Overdose of investigational medicinal product**

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Drug Accountability or Study Drug Dosing module of the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

#### **11.1.8 Safety signal detection**

Appropriate data from the study will be reviewed on an ongoing basis to detect as early as possible any safety concern(s) related to the IMP so that Investigators, clinical study subjects, regulatory authorities, and IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of AEs and (especially) any SAEs and perform ongoing SAE reconciliations in collaboration with the DS representative.

In addition, the SRG will conduct scheduled reviews of appropriate study data for the purpose of safety signal detection.

### **11.1.9 Safety Review Group**

An SRG will be established prior to the start of the study, which will comprise, at a minimum, the Study Physician(s), clinical pharmacologist, DS representative, biostatistician, Coordinating Investigator, and the [REDACTED] local Coordinating Investigator, with the intention of protecting the safety, health, and well-being of each participating subject. Individual Principal Investigators (PI, or their delegate) for each participating site will be invited when required. The precise membership, scope, and responsibilities of the SRG are described in the SRG Charter.

The SRG will meet once the first 4 subjects have completed the Transition-to-Outpatient Week (Visit 6) or withdrawn from the study before Visit 6. Subsequent meetings will occur when the first 10 subjects, the first 16 subjects, and the first 22 subjects have completed Visit 6 or withdrawn from the study before Visit 6. Thereafter, SRG meetings will be held on an as required/ad hoc basis, in response to emerging data, and at the request of any member of the SRG.

The SRG will remain blinded through the first database lock (see Section 12.3.3) unless emergent safety information requires unblinding of individual drug allocation for optimal assessment and response to AEs of concern. At the time of the first database lock, the Study Physician(s), clinical pharmacologist, DS representative, biostatistician, and other UCB personnel will be unblinded as to all subjects' treatment allocation at the beginning of the Inpatient Period.

## **11.2 Serious adverse events**

### **11.2.1 Definition of serious adverse event**

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening  
(Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious  
(Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)



- Initial inpatient hospitalization or prolongation of hospitalization, except if an extension of the Inpatient Period is required to adjust the dose of UCB0942 before discharge

(A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

### 11.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

### 11.2.3 Follow up of serious adverse events

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

Information on SAEs obtained after clinical database lock will be captured through the DS database without limitation of time.

### 11.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Potential Hy's Law, defined as  $\geq 3 \times \text{ULN}$  ALT or AST with coexisting  $\geq 2 \times \text{ULN}$  total bilirubin in the absence of  $\geq 2 \times \text{ULN}$  ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

### 11.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product

### 11.5 Anticipated serious adverse events

The following list of Anticipated SAEs has been identified, as these SAEs are anticipated to occur in the epilepsy population at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 11.2.2.

**Table 11–1: Anticipated SAEs for the epilepsy population**

MedDRA System Organ Class	MedDRA Preferred Term
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administration site conditions	Sudden unexplained death in epilepsy
Injury, poisoning, and procedural complication	Fall <sup>a</sup> , fracture <sup>a</sup> , injury <sup>a</sup>
Nervous system disorders	Cluster seizures, cognitive disorder, convulsion, incontinence <sup>a,b</sup> , status epilepticus
Pregnancy, puerperium, and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Abnormal behavior, anxiety, confusional state, psychotic behavior, sleep disorder



**Table 11–1: Anticipated SAEs for the epilepsy population**

MedDRA System Organ Class	MedDRA Preferred Term
Reproductive system and breast disorders	Impotence, menstrual disorder

MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SOC=System Organ Class

<sup>a</sup> Event is considered to be anticipated when occurring in context of seizure.

<sup>b</sup> Event is not classified in MedDRA primary SOC.

## 11.6 Laboratory measurements

Each site will use their own local clinical laboratory. The following laboratory parameters will be measured:

**Table 11–2: Laboratory measurements**

Hematology	Chemistry	Urinalysis <sup>a</sup>
Basophils	ALP	Total protein
Eosinophils	Calcium	Glucose
Lymphocytes	Chloride	pH
Monocytes	Magnesium	RBC
Neutrophils	Potassium	WBC
Hematocrit	Sodium	
Hemoglobin	Glucose	
MCH	BUN or urea	
MCHC	AST	
MCV	ALT	
Platelet count	Total bilirubin	
RBC count	LDH	
WBC count	Creatinine	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

<sup>a</sup> Dipstick test only

### 11.6.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 11.3), and, if applicable, also reported as an SAE (see Section 11.1.1).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11–3 (specific tests dependent on laboratory results and corresponding symptoms) and

consultation with a local hepatologist (if applicable; discussed in Section 11.6.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.6.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable CRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 11.6.1.2.1 are met, rechallenge with IMP may be appropriate.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

**Table 11–3: Required investigations and follow up for PDILI**

Laboratory value		Immediate			Follow up	
ALT or AST	Total bilirubin	Symptoms <sup>a</sup> of hepatitis or hypersensitivity	Consultation requirements	Actions	Testing	Evaluation
≥3xULN	≥2xULN <sup>b</sup>	NA	Hepatology consult. <sup>c</sup> Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.6.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values. <sup>d</sup>
≥8xULN	NA	NA		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN	NA	Yes		Further investigation – immediate IMP discontinuation not required (see Section 11.6.1.2).		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 11.6.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values. <sup>d</sup>

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

<sup>a</sup> Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

<sup>b</sup> If the subject also has  $\geq 2 \times$  ULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

<sup>c</sup> Details provided in Section 11.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

<sup>d</sup> Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed

### **11.6.1.1 Consultation with the Medical Monitor and local hepatologist**

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 11.6.1.3) and SAE report (if applicable).

### **11.6.1.2 Immediate action: determination of IMP discontinuation**

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 11-3 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

#### **11.6.1.2.1 IMP restart/rechallenge (if applicable)**

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 11-3), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 11.6.1.3 and Section 11.6.1.4 confirm a non-drug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed  $\geq 3 \times \text{ULN}$ .
- Subject's total bilirubin is  $< 1.5 \times \text{ULN}$ .
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician and a hepatologist. The hepatologist must be external to UCB. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the investigator-recommended monitoring plan.

### **11.6.1.3 Testing: identification/exclusion of alternative etiology**

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed

in Table 11–4 (laboratory measurements) and Table 11–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding CRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

**Table 11–4: PDILI laboratory measurements**

<b>Virology-related</b>	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
<b>Immunology</b>	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
<b>Hematology</b>	Eosinophil count
<b>Urinalysis</b>	Toxicology screen
<b>Chemistry</b>	Amylase
	If total bilirubin $\geq 1.5 \times \text{ULN}$ , obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
<b>Additional</b>	Prothrombin time/INR <sup>a</sup>
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

<sup>a</sup> Measured only for subjects with ALT  $> 8 \times \text{ULN}$ , elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia ( $> 5\%$ ), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

**Table 11–5: PDILI information to be collected**

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: <ul style="list-style-type: none"><li>• History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other “fatty liver disease”)</li><li>• Adverse reactions to drugs</li><li>• Allergies</li><li>• Relevant family history or inheritable disorders (eg, Gilbert’s syndrome, alpha-1 antitrypsin deficiency)</li><li>• Recent travel</li><li>• Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)</li></ul>
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

#### **11.6.1.4 Follow-up evaluation**

Potential drug-induced liver injury events require follow-up and monitoring as described in [Table 11–3](#). Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

### **11.7 Other safety measurements**

#### **11.7.1 Vital signs**

Vital signs including pulse rate, systolic BP, diastolic BP, respiratory rate, and body temperature (Day T1 before UCB0942 administration) will be measured in supine position, after 5 minutes of rest. Any clinically significant abnormality in the view of the Investigator will be recorded as an AE.

Vital signs will be measured at the scheduled time points presented in [Table 5-4](#).

#### **11.7.2 Electrocardiograms**

All ECG recordings will be performed with the subject resting in the supine position for at least 5 minutes. The 12-lead ECG recordings will be measured at the scheduled time points presented in [Table 5-4](#). ECG will be recorded at a speed of 25mm/s and with a calibration of 1cm/mV.



The Investigator should review all ECG recordings and, if there are abnormalities that are considered clinically significant for a particular subject, then the Investigator should initiate a review by a specialist of all ECG data pertaining to that subject. The following ECG parameters will be recorded in the eCRF: heart rate, PR-interval, QRS-duration, QT-interval, QTcB or QTcF, and Investigator's conclusion on ECG profile.

### 11.7.3 Echocardiograms

Echocardiograms will be performed during Screening, during dosing (Day OP22  $\pm$  1 week), and after the last dose of IMP (SFU7), as described in Table 5-4. The echocardiogram will be repeated at 6 months ( $\pm$  1 month) after the last dose in the following subjects:

- Subjects who complete this study but do not enter the OLE study
- Subjects who withdraw from the Outpatient Period
- Subjects who withdraw from the Inpatient Period and have an abnormal SFU7 echocardiogram

2D Doppler echocardiography will be performed with:

1. Diastolic measurements (mitral forward flow E and A waves and deceleration time)
2. Tissue Doppler on medial and lateral mitral valve annulus (S, E, and A waves)
3. Standardized views for left atrial volume measurements

Images will be recorded and stored digitally and retained if further analysis is needed. A complete echocardiography manual will be provided.

### 11.7.4 Physical examination

Physical examinations will be performed at the scheduled time points presented in Table 5-4. The physical examination will include general appearance; ear, nose, and throat; eyes, hair, and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal; hepatic; neurological (including limb reflexes); and mental status. Findings that are considered clinically significant changes since the physical examination at the Screening Visit will be recorded as AEs.

In addition, height will be measured at the Screening Visit with the subject not wearing shoes and the outcome will be rounded to the nearest 0.5cm. Body weight will be measured at the scheduled time points presented in Table 5-4. Body weight will be measured with the subject in underwear or light clothing and without wearing shoes; the outcome will be rounded to the nearest 0.1kg. At the Screening Visit, the BMI will be calculated ( $\text{weight [kg]} / [\text{height (m)}]^2$ ) and will be reported to 1 decimal place.

### 11.7.5 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Posner et al, 2011). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures (Section 5.2). The Investigator's decision about patient continuation in the study or patient withdrawal from the study if the patient has a positive response to the CSSRS Question 4, should be based on the Benefit /Risk balance for continuation or discontinuation of study treatment in view of the individual patient circumstances, condition, attained efficacy, causality, alternative risk management options, etc. Details of the case must be documented by the investigator (PI or investigator physician, not site staff conducting the CSSRS) and provided to UCB via the SAE reporting process.

### **11.7.6 Psychiatric and cognitive assessments**

The overall psychiatric condition of the subjects will be assessed at screening using the BPRS and the MINI questionnaire. The BPRS is a questionnaire consisting of 16 questions which captures the psychiatric condition of the subject.

The MINI is a widely used psychiatric structured diagnostic interview instrument. The MINI is divided into modules identified by letters corresponding to diagnostic categories. Rating is done to the right of each question by circling either Yes or No.

The MMSE is a sensitive, valid, and reliable 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment.

Further details about all questionnaires used in this study will be covered in the Study Manual.

### **11.7.7 Withdrawal monitoring**

Any symptoms of withdrawal reactions will be monitored using the CIWA-B questionnaire. The CIWA-B questionnaire contains 22 questions which are selected to distinguish withdrawal symptoms from other symptoms. Further details about this questionnaire will be covered in the Study Manual.

## **12 STUDY MANAGEMENT AND ADMINISTRATION**

### **12.1 Adherence to protocol**

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying UCB (or its representative) and the IEC in writing regarding the type of emergency and the course of action taken.

### **12.2 Monitoring**

PRA will monitor the study to meet PRA's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with PRA and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigators/institutions will permit direct access to source data/documents for study-related monitoring, audits, IEC review, and regulatory inspection(s).

The Investigator will allow PRA to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide the CRO with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

#### **12.2.1 Definition of source data**

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as echocardiogram results, must be saved and stored as instructed by UCB (or designee).

### **12.2.2 Source data verification**

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 12.2.1.

## **12.3 Data handling**

### **12.3.1 Case Report form completion**

This study is performed using remote data capture. The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

### **12.3.2 Database entry and reconciliation**

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eCRF once and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

### **12.3.3 Database lock**

The database lock and unblinding may occur in a tiered approach.

Details regarding the tiered database lock will be described in the Data Management Plan. Plans for analysis of data and production of tables, figures and listings will be described in the Statistical Analysis Plan (SAP).

### **12.3.4 Subject Screening and Enrollment log/Subject Identification Code list**

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

### **12.4 Termination of the study**

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

### **12.5 Archiving and data retention**

The Investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

### **12.6 Audit and inspection**

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned

arrangements, the protocol, investigational site, and IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

## **12.7 Good Clinical Practice**

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

## **13 STATISTICS**

A description of statistical methods follows and will be described in more detail in the SAP.

### **13.1 Definition of analysis sets**

Analysis sets will be defined as follows:

- The Enrolled Set (ES) will consist of all subjects who signed the ICF.
- The Randomized Set (RS) will consist of all enrolled subjects who were randomized.
- The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of IMP and have at least 1 post-Baseline seizure diary.
- The Per-Protocol Set (PPS) will consist of all subjects in the FAS Population who do not have a major protocol deviation impacting the primary efficacy variable.
- The Safety Set (SS) will consist of all randomized subjects who receive at least 1 dose of IMP.

All primary and secondary efficacy analyses will be carried out using the FAS.

Selected supportive efficacy analyses will be carried out using the PPS.

Safety analyses will be carried out using the SS.

All analyses will be based on randomized treatment assignment. Incorrectly-treated subjects will be evaluated during the data evaluation meeting to assess the potential impact of such cases and any special analysis considerations.

The periods considered in the definition of efficacy and safety variables are the following:

- Baseline Period consisting of 2 weeks of prospective subject diary seizure counts during the Prospective Outpatient Baseline Period
- Inpatient Double-Blind Treatment Period
  - Double-Blind Titration Week (inpatient)
  - Maintenance-Dose Week (inpatient)
  - Transition to Outpatient Week (inpatient)
- Outpatient Maintenance Period
- Last 4 weeks of Outpatient Maintenance Period
- Overall: Inpatient and Outpatient Period



## 13.2 General statistical considerations

Summary statistics will be provided for all efficacy, safety, and Baseline/demographic variables. Summary statistics will consist of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation [SD], minimum, maximum, 25th and 75th percentiles) will be tabulated. Unless otherwise mentioned, statistical hypothesis tests will be one-sided at the 5% significance level.

## 13.3 Planned efficacy analyses

The efficacy variables will be analyzed as described below using the FAS.

Total seizure frequency per week (7 days) will be derived from the seizure count information recorded on the diary card and is defined as the number of seizures standardized to a 7-day period. It is computed as the number of seizures recorded (by category: total, type I, type IA1, IB, and IC) over the period, divided by the total number of days in that period multiplied by 7.

### 13.3.1 Analysis of the primary efficacy variable

The primary outcome measure is the 75%RR. In the active group, this is defined as the proportion of subjects with a 75% or greater reduction in focal seizure frequency during the last 2 weeks of the Inpatient Period compared to the 2-week Prospective Outpatient Baseline Period. In the placebo group, the 75%RR is defined as the proportion of subjects with a 75% or greater reduction in focal seizure frequency during the first 2 weeks of the Inpatient Period (the 2 weeks on placebo) compared to the Prospective Outpatient Baseline Period. The 75%RR will be analyzed using a logistic regression with effects for treatment, for LEV use stratification factor, and log-transformed Baseline seizure frequency as a continuous covariate. Odds-ratio of UCB0942 versus placebo groups and its 95% confidence intervals (CI) will be estimated. The primary analysis will be performed on the FAS but also on the PPS.

### 13.3.2 Secondary efficacy analyses

#### Median percent reduction in seizures:

The percent reduction in total and partial seizure frequency from Baseline to the corresponding Treatment Period will be compared between UCB0942 arm and placebo using a Wilcoxon-Mann-Whitney test. The Hodges-Lehmann non-parametric estimator will be used to estimate the median percent reduction in seizures between groups and its corresponding 95% CI will be provided. For secondary efficacy variables using responder rate (75%RR and 50%RR), the analysis will be conducted similarly to the primary efficacy analysis (Section 13.3.1). Different treatment periods will be considered (inpatient as defined in Section 13.3.1, outpatient, and overall).

#### Seizure freedom:

To be considered seizure free, a subject must not report seizures of any type and must complete the corresponding treatment period. The seizure freedom rate will be analyzed using a logistic regression with effects for treatment and log-transformed Baseline seizure frequency as a continuous covariate. Odds-ratio of UCB0942 versus placebo groups and its 95% CIs will be estimated. The seizure freedom will be evaluated at the following different treatment times: Inpatient Period as defined in Section 13.3.1, last 4 weeks of Outpatient Maintenance Period.



### Percentage of seizure-free days:

A descriptive analysis will be performed on the percentage of seizure-free days by treatment group and study periods.

### **13.3.3 Exploratory efficacy analyses**

#### Seizure severity:

Changes in the SSQ and average seizure severity as calculated by the percentage of seizures that are type IC from Baseline to the end of the Inpatient Period and the end of the Outpatient Maintenance Period will be analyzed.

The QOLIE-31-P (change from Baseline) will be analyzed by descriptive statistics and any relevant graphical displays. Relationship between QOLIE-31-P parameters and efficacy parameters (seizure reduction, 75%RR) will be evaluated.

#### Seizure frequency (continuous variable):

An analysis of covariance (ANCOVA) will be performed on the log-transformed weekly seizure frequency data. Specifically,  $\ln(1 + \text{weekly seizure frequency during the Treatment Period})$  will be modeled with treatment group as factor and  $\ln(1 + \text{weekly seizure frequency at Baseline})$  as covariate. Contrasts will be estimated to compare UCB0942 to observed placebo results.

All seizure frequency (Type I+II+III) and subtypes of partial seizures (Type IA, IB, IC) per week over the Treatment Period will be analyzed in a manner similar to the seizure frequency. Transformation of efficacy data could be envisaged given the data distribution. Different treatment periods will be considered (inpatient as defined in Section 13.3.1, outpatient, and overall).

Box-plots will be also displayed for the change in seizure frequency (absolute and percentage).

Exploratory analysis will be performed on the seizure count/SSQ data collected during the Tapering/Safety Follow-Up Period.

### **13.4 Planned safety and population PK analyses**

#### **13.4.1 Safety analyses**

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be summarized by MedDRA System Organ Class and Preferred Term. The incidence of SAEs, AEs leading to premature discontinuation or dose tapering, and related AEs, and the incidence of AEs by maximum intensity, will also be summarized.

Laboratory values, ECG data (ventricular rate, PR, QTc [using Bazett's and Fridericia's formula], and QRS), vital signs, weight, and changes from Baseline in these measures will be summarized by period, visit, and treatment group. Possibly clinically significant treatment-emergent abnormalities for laboratory values, vital signs, and weight will be listed and summarized by period and visit for each treatment group.

Electrocardiogram abnormalities as well as physical and neurological abnormalities will also be listed by period and visit. Quantitative safety parameters will be summarized descriptively by time point and treatment group. Categorical safety summaries will provide the number and percentage of subjects within each summarized category. Doppler echocardiography results

at Baseline and during and after treatment, and changes from Baseline, will be listed and descriptively summarized.

All C-SSRS data obtained at Baseline and subsequent visits will be reported as a listing ordered by subject and visit. Psychiatric and cognitive assessments (MINI, BPRS, and MMSE) and CIWA-B data will also be covered using listings. Moreover, hypersensitivity reactions data will be summarized and listed.

### **13.4.2 PK analyses**

#### **13.4.2.1 Non-compartmental PK analysis**

Plasma concentrations of UCB0942, [REDACTED] will be determined from blood samples obtained in the study, during the Titration and Maintenance Periods in order to investigate the PK of UCB0942 and its major metabolites.

The following PK parameters will be calculated:

- $AUC_{\tau}$ : area under the plasma concentration-time curve over a dosing interval, as determined using the linear trapezoidal rule.
- $C_{max}$ : maximum observed plasma concentration.
- $t_{max}$ : time of  $C_{max}$ .
- $t_{1/2}$ : apparent terminal elimination half-life, reported in hours, as determined via simple linear regression (slope =  $-\lambda_z$ ) of natural log(ln) concentration vs time for data points in the terminal phase of the concentration-time curve.  $t_{1/2}$  is calculated as  $\ln(2)/\lambda_z$ .
- $C_{trough}$ : measured concentration at the end of the dosing interval at steady state.

The PK variables will be computed by non-compartmental analysis (NCA) with Phoenix WinNonlin (version 6.2 or higher) using the actual sampling times. The linear trapezoidal method will be used to calculate AUC parameters.

PK parameters of UCB0942 and its metabolites will be listed and summarized using the following descriptive statistics: number of observations, geometric mean, lower and upper 95% CI, geometric coefficient of variation (CV), arithmetic mean, SD, median, and minimum and maximum values. Graphical outputs over time will be produced on the trough plasma drug concentrations.

#### **13.4.2.2 Population PK analysis**

If appropriate, a population PK analysis will be conducted to characterize the PK of UCB0942, including inter-individual variability, and to assess the potential effect of concomitant AEDs on the PK of UCB0942. The population PK analysis will be based on plasma concentrations obtained during the Maintenance Week of the Inpatient Period, as well as samples collected during the Outpatient Maintenance Period. A separate data analysis plan (DAP) will describe the analysis, which will be reported in a separate report.

#### **13.4.2.3 Population PK-PD analysis**

Exploratory population PK-PD analysis may be performed if needed to characterize the relationship between exposure to UCB0942 and the clinical and/or safety clinical outcome. A separate DAP will describe the analysis, which will be reported in a separate report.

### 13.5 Handling of protocol deviations

After all lockable data have been verified/entered into a database and prior to the first database lock, a data evaluation meeting will take place. The purpose of the data evaluation will be to examine all protocol deviations, define the PPS, and to verify the quality of the data. The data evaluation will also help in guiding decisions on how to manage data issues on a case-by-case basis (eg, withdrawals, dropouts, and protocol deviations).

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the Study Master File. After the data review, resolution of all issues, and documentation of all decisions, the database will be locked.

### 13.6 Handling of dropouts or missing data

The methods for handling dropouts will be described in the SAP.

### 13.7 Planned interim analyses and data monitoring

An interim analysis will be performed if needed for purposes of planning and designing of future studies. If performed, this analysis will be conducted when at least 75% of patients have been randomized and completed through the Inpatient Period (completed through Visit 5).

All subjects who have completed through Visit 5 at the time of the data snapshot will be included in the interim analysis.

All statistical analyses will be described in detail in the interim SAP.

For the interim analysis, the primary efficacy variable (75%RR) will be analyzed using the methods described for the primary efficacy analysis. In addition, seizure-free rate, 50%RR, and percent reduction in focal seizure frequency will be analyzed as described for the secondary/exploratory analyses.

The 75%RR, Seizure-free rate, and 50%RR variables may also be analyzed using Bayesian logistic regression. If Bayesian analysis is performed, the percent reduction in focal seizure frequency from the Baseline will be estimated using Bayesian analysis of variance (ANOVA) and/or ANCOVA. For these analyses, posterior medians, 95% credible intervals for the treatment effect, and additional posterior probabilities will be presented. Non informative and informative priors will be considered, and sensitivity to different prior settings will be assessed. Other efficacy variables may also be analyzed in the Bayesian framework.

The following safety data will also be presented:

- Treatment emergent AEs
- AEs leading to drop-out or withdrawal
- SAEs
- Laboratory assessments out of normal range
- BPRS

The study will not be terminated early for either efficacy or futility based on the results of this interim analysis and therefore, an alpha penalty of 0.001 to be assessed on the primary efficacy analysis is considered appropriate.

The study is not expected to be stopped due to safety reasons during this interim analysis, since there are ongoing quarterly Safety Review Group meetings already planned for this purpose. Therefore, no criteria for evaluation of early stopping due to safety are included.

An unblinded team will be established at both the Sponsor and CRO and will include the following roles (all unblinded): Data Manager, Statistician, Statistical Programmer, and Project Lead. All staff involved in the conduct of the study, including staff at UCB, the CRO, participating vendors, and the participating sites will remain blinded to individual treatment identity and will not be informed of the results of the interim analysis until final unblinding.

### **13.8 Determination of sample size**

This is an exploratory pilot study to obtain a first evaluation of the efficacy (estimate and variability) of UCB0942 in this specific refractory population. The planned sample size was evaluated based on placebo results obtained in similar refractory epileptic populations from BRV and lacosamide Phase 3 studies in add-on partial epilepsy, and the desired effect was based on a doubling of the effect of lacosamide and BRV in subjects in the current target population.

For the primary efficacy variable, the 75%RR in the placebo group from these historical studies was estimated to be less than 5%. The response on UCB0942 was expected to be 36.5% in order to provide clear differentiation from lacosamide and BRV in this patient population.

Based on a 2-group Fisher's exact one-sided test with a ratio active:placebo of 1:1, the required number of subjects is 23 in each arm to detect a significant difference between the 2 groups with a power of 80% and a false positive rate of 5%.

## **14 ETHICS AND REGULATORY REQUIREMENTS**

### **14.1 Informed consent**

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the written ICF should be signed and personally dated by the subject or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IEC review, and regulatory inspection.

If the ICF is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IEC and use of the amended form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

## **14.2 Subject identification cards**

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

## **14.3 Subject compensation**

In addition to reimbursement of incurred expenses (eg, travel), subjects will be financially compensated for the burden and inconvenience of spending time at the inpatient unit as this is an unusual requirement for participants in clinical studies. The amount of compensation will be country-specific and approved by the local ethics committee.

## **14.4 Independent Ethics Committees**

The study will be conducted under the auspices of an IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IEC for the protocol.

The Investigator will also promptly report to the IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IEC as allowed.

As part of the IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IEC (based on IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The Investigator should provide a final report to the IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IEC notification.



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## **14.5 Subject privacy**

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

## **14.6 Protocol amendments**

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IECs, and the regulatory authorities (if required), prior to being implemented.

## **15 FINANCE, INSURANCE, AND PUBLICATION**

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.



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## **17 APPENDICES**

### **17.1 Protocol Amendment 1.0**

#### **Rationale for the amendment**

The addition of an echocardiogram during dosing was made as a result of comments from the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte). They have requested the addition of an echocardiogram during dosing. This echocardiogram has been added at Day OP22. In addition, the following changes were made:

- It has been clarified that either urine or serum pregnancy tests can be used for all visits.
- It has been pointed out that the decision to continue in the OLE will occur at Day OP43.
- Clarification on the procedure for dose reduction in cases of poor tolerability of UCB0942 400mg bid (ie, reduction to UCB0942 200mg bid and in some cases to UCB0942 100mg bid).
- The withdrawal criteria for elevated transaminases have been reworded as the previous description was not clear.

#### **Modifications and changes**

##### **Specific changes**

##### **Change #1**

##### **Section 1 SUMMARY, bullet #7**

- An echocardiogram at the end of the study and at 6 months after the final dose

##### **Has been changed to:**

- An echocardiogram during dosing, after the last dose, and at 6 months after the final dose

##### **Change #2**

##### **Section 1 SUMMARY, paragraph 6**

Titration to UCB0942 400mg bid will occur over the course of 1 week in the clinical unit. For subjects in the active arm, doses will be titrated to UCB0942 400mg bid during the first inpatient week. For subjects who initially received placebo, doses will be titrated to UCB0942 400mg bid during the last week of the Inpatient Period. For subjects in the active arm who do not tolerate UCB0942 400mg bid, during the third week of the Inpatient Period, the dose can be tapered to UCB0942 200mg bid before starting the Outpatient Maintenance Period. Similarly, for subjects in the placebo group the dose can be tapered to a tolerable dose during the Outpatient Maintenance Period. All subjects will stay in the clinical unit for a total of 3 weeks and will then be discharged for an 8-week Outpatient Maintenance Period.

##### **Has been changed to:**

Titration to UCB0942 400mg bid will occur over the course of 1 week in the clinical unit. For subjects in the active arm, doses will be titrated to UCB0942 400mg bid during the first inpatient week. For subjects who initially received placebo, doses will be titrated to UCB0942 400mg bid during the last week of the Inpatient Period. For subjects in the active

arm who do not tolerate UCB0942 400mg bid, during the third week of the Inpatient Period, the dose can be tapered to UCB0942 200mg bid before starting the Outpatient Maintenance Period. Similarly, for subjects in the placebo group the dose can be tapered to UCB0942 200mg bid during the Outpatient Maintenance Period. Dose tapering to UCB0942 100mg bid may be permitted after discussion with the Sponsor's Study Physician. All subjects will stay in the clinical unit for a total of 3 weeks and will then be discharged for an 8-week Outpatient Maintenance Period.

### **Change #3**

#### **Section 4.1.3 Exploratory efficacy variables, bullet #4**

- Change in time to recovery from Baseline to the end of the Inpatient Period and the end of the Outpatient Maintenance Period (derived from the SSQ, see Section 9.2).

**Has been deleted**

### **Change #4**

#### **Section 4.4 Safety variables, bullet #10**

- Changes in 2-dimensional Doppler echocardiography from Baseline to after treatment (end of dosing and 6 months after last dose), with diastolic measurements as well as atrial volumes to identify any subtle valvular changes and to assess for pericardial effusions

**Has been changed to:**

- Changes in 2-dimensional Doppler echocardiography from Baseline to after Baseline (during dosing, after the last dose, and 6 months after last dose), with diastolic measurements as well as atrial volumes to identify any subtle valvular changes and to assess for pericardial effusions

### **Change #5**

#### **Section 5.1 Study description, bullet #7**

- An echocardiogram at the end of the study and at 6 months after the last dose

**Has been changed to:**

- An echocardiogram during dosing, after the last dose, and at 6 months after the last dose

### **Change #6**

#### **Section 5.1 Study description, paragraph 6**

If a subject is not tolerating UCB0942 400mg bid well, the dose can be tapered to UCB0942 200mg bid. The taper from UCB0942 400mg bid to UCB0942 200mg bid will occur over 3 days (see [Table 5-2](#)) and will require unblinding of the subject if this occurs during the Inpatient Period.

**Has been changed to:**

If a subject is not tolerating UCB0942 400mg bid well, the dose can be tapered to UCB0942 200mg bid. The taper from UCB0942 400mg bid to UCB0942 200mg bid will occur over 3 days (see [Table 5-2](#)) and will require unblinding of the subject if this occurs during the Inpatient Period. Dose tapering to UCB0942 100mg bid may be permitted after discussion with the Sponsor's Study Physician.

## Change #7

### Section 5.1.2 Planned number of subjects and sites

Subjects with highly drug-resistant focal epilepsy will be enrolled at up to 10 [REDACTED] sites in order to provide 46 evaluable subjects, ie, 46 subjects who complete the Inpatient Period. Subjects who drop out before Visit 6 (eg, during the Inpatient Period) for reasons other than safety or tolerability will be replaced. First subject, first visit is planned for Q2 2015.

#### Has been changed to:

Subjects with highly drug-resistant focal epilepsy will be enrolled at [REDACTED] sites in order to provide 46 evaluable subjects, ie, 46 subjects who complete the Inpatient Period. Subjects who drop out before Visit 6 (eg, during the Inpatient Period) for reasons other than safety or tolerability will be replaced. First subject, first visit is planned for Q2 2015.

## Change #8

### Section 5.2 Schedule of study assessments

In the schedule of study assessments (Table 5-4), an “X” has been added at Day OP22 for echocardiogram.

## Change #9

### Section 5.2 Schedule of study assessments, Table 5-4, footnote j:

<sup>j</sup> In addition to the echocardiogram after the last dose, for subjects who do not continue in the OLE study, an echocardiogram at 6 months after the last dose will also be performed.

#### Has been changed to:

<sup>j</sup> In addition to the echocardiogram during dosing and after the last dose, for subjects who do not continue in the OLE study, an echocardiogram at 6 months after the last dose will also be performed. Please note that the during dosing time point of Day OP22 for the echocardiogram has a time window of  $\pm 1$  week instead of  $\pm 2$  days.

## Change #10

### Section 5.2 Schedule of study assessments, Table 5-4, footnote l:

<sup>l</sup> Serum pregnancy test at Screening and admission (Day T1); urine pregnancy test at all other occasions.

#### Has been changed to:

<sup>l</sup> Urine or serum pregnancy test.

## Change #11

### Section 5.2 Schedule of study assessments, Table 5-5, footnote h:

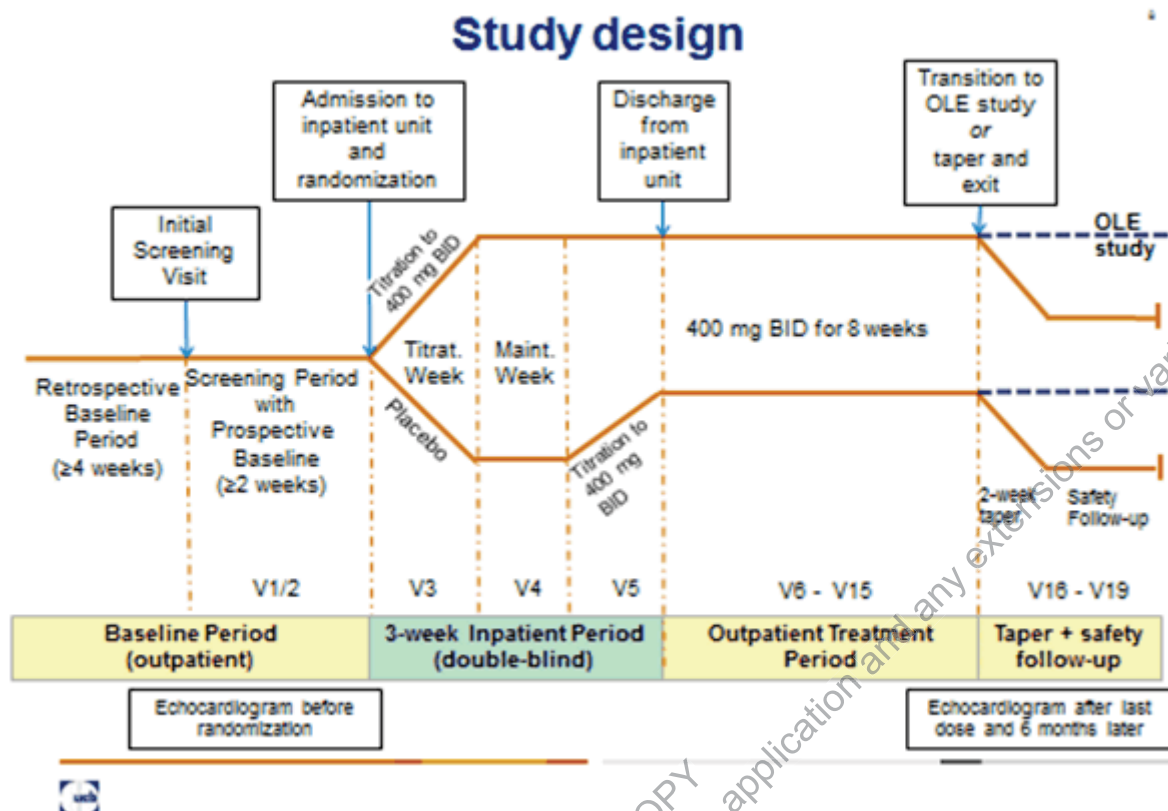
<sup>h</sup> Serum pregnancy test, female subject only.

#### Has been changed to:

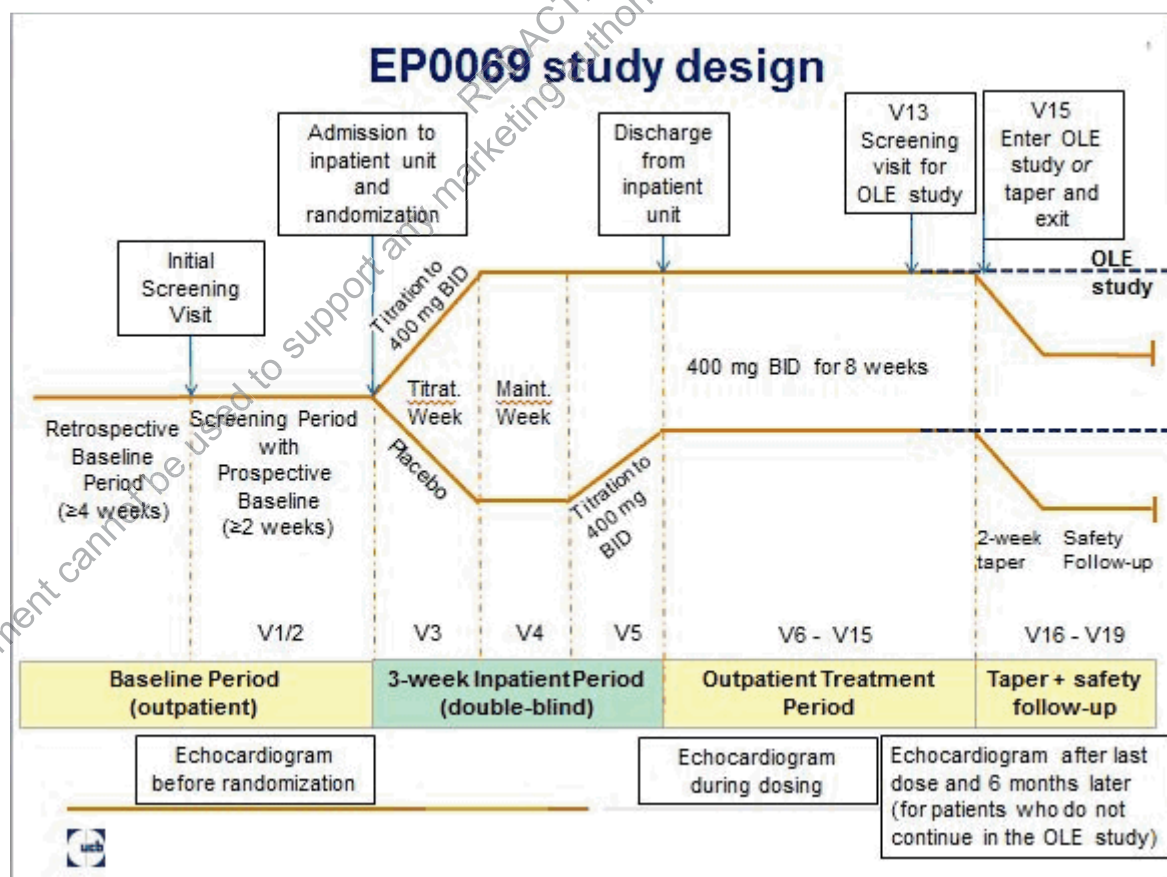
<sup>h</sup> Urine or serum pregnancy test, female subject only.

## Change #12

### Section 5.3 Schematic diagram



Has been changed to:





## Change #13

### Section 6.3 Withdrawal criteria, criterion #1

Subject develops a clinically relevant medical condition (or laboratory abnormality) that, in the opinion of the Investigator, compromises the subject's ability to participate or safety. In the case of transaminase (AST, ALT, or both) levels at least 3 times the upper limit of normal (ULN) to less than 5 times the ULN, in the presence of normal total bilirubin, the laboratory tests will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are at least 3 times the ULN to less than 5 times the ULN with normal bilirubin), then weekly monitoring of liver function tests should continue until resolved (ie, less than 3 times the ULN or stable condition). The Investigator is to decide whether or not to stop the investigational medicinal product (IMP). To monitor for hypersensitivity reactions, percent eosinophils >10% or absolute eosinophil count  $\geq 0.5$ G/L or absolute neutrophil count <1.5G/L or absolute platelet count  $\leq 100$ G/L, if in combination with fever, rash, lymphadenopathy, or other symptoms/signs suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, or arthritis) will lead to stopping the IMP.

#### Has been changed to:

Subject develops a clinically relevant medical condition (or laboratory abnormality) that, in the opinion of the Investigator, compromises the subject's ability to participate or safety. In the case of transaminase (AST, ALT, or both) levels at least 3 times the upper limit of normal (ULN) in the presence of normal total bilirubin, the laboratory tests will be repeated within a few days. If the repeat testing confirms the abnormality, then weekly monitoring of liver function tests should continue until resolved (ie, less than 3 times the ULN or stable condition). The Investigator is to decide whether or not to stop the investigational medicinal product (IMP). To monitor for hypersensitivity reactions, percent eosinophils >10% or absolute eosinophil count  $\geq 0.5$ G/L or absolute neutrophil count <1.5G/L or absolute platelet count  $\leq 100$ G/L, if in combination with fever, rash, lymphadenopathy, or other symptoms/signs suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, or arthritis) will lead to stopping the IMP.

## Change #14

### Section 7.1 Description of investigational medicinal products, Table 7-1, Note

For the Inpatient Period, 1 kit per treatment period and per dose will be packaged. Each kit will contain blister packs, each covering 1 week of treatment. For the Outpatient Period, UCB0942 tablets will be provided in bottles, containing 40 tablets per bottle, either 200mg tablets for subjects on UCB0942 400mg bid, or 100mg tablets for subjects who reduce dose to UCB0942 200mg bid. The bottles containing 40 UCB0942 100mg tablets will be dispensed for the Taper Period.

#### Has been changed to:

For the Inpatient Period, 1 kit per treatment period and per dose will be packaged. Each kit will contain blister packs, each covering 1 week of treatment. For the Outpatient Period, UCB0942 tablets will be provided in bottles, containing 37 tablets per bottle, either 200mg tablets for subjects on UCB0942 400mg bid, or 100mg tablets for subjects who reduce dose



to UCB0942 200mg bid. The bottles containing 37 UCB0942 100mg tablets will be dispensed for the Taper Period.

### **Change #15**

#### **Section 7.9.1.3 Breaking the treatment blind for taper of dose during the study**

If the IMP is not tolerated during the Inpatient Period by an individual subject, the dose can be tapered to the last tolerated dose. This is only permitted if the subject has great difficulty tolerating the IMP and the Investigator does not think that tolerability will improve. When it is decided to reduce the dose, the blind will have to be broken, following the procedure described in Section 7.9.1.2.

#### **Has been changed to:**

If the IMP is not tolerated during the Inpatient Period by an individual subject, the dose can be tapered to UCB0942 200mg bid. This is only permitted if the subject has great difficulty tolerating the IMP and the Investigator does not think that tolerability will improve. When it is decided to reduce the dose, the blind will have to be broken, following the procedure described in Section 7.9.1.2.

### **Change #16**

#### **Section 8.1.1 Screening (Visit 1, Day -1), bullet #16**

- Serum pregnancy test (female subjects only)

#### **Has been changed to:**

- Urine or serum pregnancy test (female subjects only)

### **Change #17**

#### **Section 8.2.1 Titration Week (Visit 3, Day T1 to Day T7), bullet #5**

- Serum pregnancy test (female subjects only)

#### **Has been changed to:**

- Urine or serum pregnancy test (female subjects only)

### **Change #18**

#### **Section 8.3.1 Outpatient Maintenance Period (Visit 6 to Visit 15, Day OP1 to Day OP57), paragraph 4**

Further dose tapering may be implemented for each subject during the 8 weeks of treatment in the Outpatient Maintenance Period at the discretion of the Investigator in conjunction with the wishes of the subject.

#### **Has been changed to:**

Dose tapering from UCB0942 400mg bid to UCB0942 200mg bid to increase tolerability may be implemented for each subject at any time during the 8 weeks of treatment in the Outpatient Maintenance Period at the discretion of the Investigator in conjunction with the wishes of the subject. Dose tapering to UCB0942 100mg bid may be permitted after discussion with the Sponsor's Study Physician.

---

**And the following bullet point has been added:**

- Echocardiogram (Day OP22  $\pm$ 1 week)

**Change #19**

**Section 8.3.1 Outpatient Maintenance Period (Visit 6 to Visit 15, Day OP1 to Day OP57), BULLET #13**

- Urine pregnancy test (females only; Days OP8, OP36, and OP57)

**Has been changed to:**

- Urine or serum pregnancy test (females only; Days OP8, OP36, and OP57)

**And the following bullet point has been added:**

- Decision to continue in the OLE study (Day OP43)

**Change #20**

**Section 8.3.3 Safety Follow-Up (Visit 18 to 20, Day SFU7, SFU14, and SFU28), BULLET #9**

- Pregnancy test (urine, females only)

**Has been changed to:**

- Pregnancy test (urine or serum, females only)

**Change #21**

**Section 8.3.4 Echocardiography follow up**

For subjects who do not continue in the OLE study, it is mandatory that they have an echocardiogram at 6 months ( $\pm$ 1 month) after the last dose of IMP (in addition to the echocardiogram at the end of the study).

**Has been changed to:**

For subjects who do not continue in the OLE study, it is mandatory that they have an echocardiogram at 6 months ( $\pm$ 1 month) after the last dose of IMP (in addition to the echocardiogram at Screening, during dosing, and after the last dose).

**Change #22**

**Section 8.4 Withdrawal Visit, bullet #18**

- Pregnancy test (serum, females only)

**Has been changed to:**

- Pregnancy test (urine or serum, females only)

**Change #23**

**Section 8.6 Open-label extension study (EP0073)**

Subjects who experience substantial benefit from UCB0942 with acceptable tolerability will have the option to continue taking UCB0942 during an OLE study. The decision to enter the OLE study must be made by the subject in consultation with the Investigator and/or the subject's habitual epilepsy provider (the neurologist who treats the subject outside of the study), and this decision must take into account the benefit experienced, the potential risks of

long-term exposure to UCB0942, and the potential benefit and risks of other treatment options available that have not been tried. Subjects who enter the OLE study will have echocardiographic follow up as scheduled in the OLE study protocol and will therefore not participate in the echocardiographic follow up described in Section 8.3.4.

**Has been changed to:**

Subjects who experience substantial benefit from UCB0942 with acceptable tolerability may have the option to continue taking UCB0942 during an OLE study. The decision to enter the OLE study must be made by the subject in consultation with the Investigator and/or the subject's caregiver. This decision must take into account the benefit experienced, the potential risks of long-term exposure to UCB0942, and the potential benefit and risks of other treatment options available. Subjects who enter the OLE study will have echocardiographic follow up as scheduled in the OLE study protocol and will therefore not participate in the echocardiographic follow up described in Section 8.3.4.

**Change #24**

**Section 9.2 Seizure Severity Questionnaire, paragraph 3**

The SSQ will be completed according to the tabular schedule of study procedures, [Table 5-4](#). For this study the recall period will be set to 1 week rather than the original 4 weeks. At the very beginning of the visit, the SSQ will be provided to all subjects. The subject will be asked to complete the questionnaire on his/her own. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the SSQ will be covered in the Study Manual.

**Has been changed to:**

The SSQ will be completed according to the tabular schedule of study procedures, [Table 5-4](#). For this study the recall period will be set to 1 week rather than the original 4 weeks. At the very beginning of the visit, the SSQ will be provided to all subjects. The subject will be asked to complete the questionnaire on his/her own. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the SSQ will be covered in the Study Manual.

**Change #25**

**Section 11.7.3 Echocardiograms, paragraph 1**

Echocardiograms will be performed during Screening, after the last dose of IMP, and at 6 months after the last dose of IMP, as described in [Table 5-4](#).

**Has been changed to:**

Echocardiograms will be performed during Screening, during dosing (Day OP22  $\pm$  1 week), after the last dose of IMP, and at 6 months after the last dose of IMP, as described in [Table 5-4](#).

**Change #26**

**Section 13.3.3 Exploratory efficacy analyses, paragraph 1**

Changes in the SSQ, time to recovery, and average seizure severity as calculated by the percentage of seizures that are type IC from Baseline to the end of the Inpatient Period and the end of the Outpatient Maintenance Period will be analyzed.

---

**Has been changed to:**

Changes in the SSQ and average seizure severity as calculated by the percentage of seizures that are type IC from Baseline to the end of the Inpatient Period and the end of the Outpatient Maintenance Period will be analyzed.

**Change #27****Section 13.4.1 Safety analyses, paragraph 3**

Electrocardiogram abnormalities as well as physical and neurological abnormalities will also be listed by period and visit. Quantitative safety parameters will be summarized descriptively by time point and treatment group. Categorical safety summaries will provide the number and percentage of subjects within each summarized category. Doppler echocardiography results at Baseline and after treatment, and changes from Baseline, will be listed and descriptively summarized.

**Has been changed to:**

Electrocardiogram abnormalities as well as physical and neurological abnormalities will also be listed by period and visit. Quantitative safety parameters will be summarized descriptively by time point and treatment group. Categorical safety summaries will provide the number and percentage of subjects within each summarized category. Doppler echocardiography results at Baseline and during and after treatment, and changes from Baseline, will be listed and descriptively summarized.

## **17.2 Protocol Amendment 2.0**

### **Rationale for the amendment**

The protocol describes the use of video monitoring during the Inpatient Period. The video monitoring is an exploratory endpoint, and the data will be used to assess the difference between seizure diaries (the primary endpoint) and seizures detected with video. The intention of the protocol language was to let sites perform video monitoring according to their usual clinical practice; however, the language in the first version was not sufficiently clear to convey this flexibility. The purpose of this amendment is to make the video monitoring language in the protocol more flexible so that sites/Investigators can perform this according to their usual practice. This new language will also allow video-EEG monitoring as some sites do not perform video-only monitoring.

A second change was the wording of the drug misuse exclusion criterion. As is customary in most UCB protocols, exclusion for drug misuse is only applicable if the Investigator deems that study participation is either a risk to the subject or that the drug misuse could confound the outcomes measured in the study. The wording of this exclusion criterion was changed to match that of other UCB studies.

In addition, the possibility of rescreening screening failures was added.

### **Modifications and changes**

#### **Specific changes**

##### **Change #1**

##### **Section 3.3 Exploratory objectives, bullet #2**

Use video recordings to explore the effect of UCB0942 on seizure type, seizure severity, seizure duration, and duration of the postictal period

##### **Has been changed to:**

Use video recordings, when available, to explore the effect of UCB0942 on seizure type, seizure severity, seizure duration, and duration of the postictal period

##### **Change #2**

##### **Section 4.3, Exploratory variables, paragraph 4**

During the Inpatient Period, there will be video monitoring of subjects in their rooms (and in other areas depending on the infrastructure of each site) to assess seizure type, severity, duration, and the duration of the postictal period.

##### **Has been changed to:**

At the discretion of the Investigator, sites may or may not perform video or video- electroencephalogram (EEG) monitoring during parts of the Inpatient Period or during the whole Inpatient Period, depending on the infrastructure of each site, to assess seizure type, severity, duration, and the duration of the postictal period.

##### **Change #3**

##### **Section 5.2 Schedule of study assessments, Table 5-4, footnote a:**

If a subject fails screening, a rescreening is allowed if deemed appropriate by the Investigator.

**Has been added, subsequent footnotes have been renumbered accordingly**

**Change #4**

**Section 5.2 Schedule of study assessments, Table 5-4:**

Video monitoring in subject rooms

**Has been changed to:**

Video or video-EEG monitoring<sup>m</sup>

**Change #5**

**Section 5.2 Schedule of study assessments, Table 5-4:**

EEG=electroencephalogram;

**Has been added**

**Change #6**

**Section 5.2 Schedule of study assessments, Table 5-4, footnote m:**

At the discretion of the Investigator, sites may or may not perform video or video-EEG monitoring during parts of the Inpatient Period or during the whole Inpatient Period.

**Has been added, subsequent footnotes have been renumbered accordingly**

**Change #7**

**Section 5.2 Schedule of study assessments, Table 5-5:**

Video monitoring in subject rooms

**Has been changed to:**

Video or video-EEG monitoring<sup>h</sup>

**Change #8**

**Section 5.2 Schedule of study assessments, Table 5-5:**

EEG=electroencephalogram;

**Has been added**

**Changes #9**

**Section 5.2 Schedule of study assessments, Table 5-5, footnote h:**

At the discretion of the Investigator, sites may or may not perform video or video-EEG monitoring during parts of the Inpatient Period or during the whole Inpatient Period.

**Has been added, subsequent footnotes have been renumbered accordingly**

**Change #10**

**Section 6.2 Exclusion criteria, criterion #18**



18. Subject has a history in the last 5 years of drug or alcohol dependency or tests positive for drugs of abuse or alcohol during Screening.

**Has been changed to:**

18. Subject has past or present substance abuse/dependence that in the opinion of the Investigator could threaten the subject's safety within the study, affect the subject's ability to fully participate in the study, or confound study interpretation.

**Change #11**

**Section 8.1.2 Baseline Period (Visit 2, Day BL1 to BL14-21)**

If a subject fails screening, a rescreening is allowed if deemed appropriate by the Investigator.

**Has been added**

**Change #12**

**Section 8.2.1 Titration Week (Visit 3, Day T1 to Day T7)**

During the Inpatient Period of the study, all subjects will be monitored by video in their bedrooms (and at some sites in other areas) to provide objective data on seizure type, severity, and duration, and on the duration of the postictal period as an exploratory outcome measure.

**Has been changed to:**

At the discretion of the Investigator, sites may or may not perform video or video-EEG monitoring during parts of the Inpatient Period or during the whole Inpatient Period of the study, depending on the infrastructure of each site, to provide objective data on seizure type, severity, and duration, and on the duration of the postictal period as an exploratory outcome measure.

**Change #13**

**Section 8.2.1 Titration Week (Visit 3, Day T1 to Day T7)**

- Video seizure monitoring in subject rooms

**Has been changed to:**

- Video or video-EEG monitoring (optional)

**Change #14**

**Section 8.2.2 Maintenance-Dose Week (Visit 4, Day MD1 to Day MD7)**

At the end of the Titration Week, subjects continue in the Maintenance-Dose Week, during which they will continue to record their seizures in subject diaries and will continue to be video-monitored in their bedrooms.

**Has been changed to:**

At the end of the Titration Week, subjects continue in the Maintenance-Dose Week, during which they will continue to record their seizures in subject diaries.

**Change #15**

**Section 8.2.2 Maintenance-Dose Week (Visit 4, Day MD1 to Day MD7)**

- Video monitoring in subject rooms

**Has been changed to:**

- Video or video-EEG monitoring (optional)

**Change #16**

**Section 8.2.3 Transition-to-Outpatient Week (Visit 5, Day TTO1 to Day TTO7)**

- Video monitoring

**Has been changed to:**

- Video or video-EEG monitoring (optional)

**Change #17**

**Section 9.1.1 Video monitoring**

During all inpatient periods, there will be continuous video monitoring in subjects' rooms (and at some sites in other areas) to allow exploratory analysis of seizure type, severity, and duration, and of the duration of the postictal period.

**Has been changed to:**

At the discretion of the Investigator, sites may or may not perform video or video-EEG monitoring during part of the Inpatient Period or during the whole Inpatient Period, depending on the infrastructure of each site, to allow exploratory analysis of seizure type, severity, and duration, and of the duration of the postictal period.

**17.3 Protocol Amendment 3.0**

**Rationale for the Amendment**

The primary reason for Amendment 3 is to add and describe an optional interim analysis for purposes of planning and designing of future studies.

Other reasons for the amendment include the following:

- To add an exploratory objective, variable and associated assessment (diary addendum). Note that this was already part of the study, but not clearly described in the protocol.
- To clarify procedures for dosing when there is intolerance to study medication during the Inpatient Period
- To allow and specify flexibility in dosing during the Outpatient Maintenance Period
- To further specify which Subjects require an echocardiogram at 6 months after the last dose of study medication
- To expand the range of BMIs allowed for inclusion in the study
- To revise procedures for assessment of suicidality using the C-SSRS (specifically, the C-SSRS withdrawal criterion) in line with revision to sop-ai-015774, Version 2.0, which became effective on 01 Apr 2016.
- To update the protocol information pertaining to potential drug-induced liver injury (exclusion criteria, withdrawal criteria, adverse events of special interest, and

assessments) based on new standard language which is being applied across all protocols at UCB. Note that these additions do not reflect a change in the known safety of the compound.

- To revise study personnel and make other administrative changes

## Modifications and changes

### Specific changes

#### Change #1

##### Coordinating Investigator [REDACTED]

Name:	Dr. [REDACTED]
Affiliation:	[REDACTED]
Address:	[REDACTED] [REDACTED] [REDACTED]
Phone:	+ [REDACTED]

#### Has been changed to:

##### Coordinating Investigator [REDACTED]

Name:	Prof. Dr. [REDACTED]
Affiliation:	[REDACTED]
Address:	[REDACTED] [REDACTED] [REDACTED]
Phone:	[REDACTED]

#### Change #2

##### Study Contact Information, Early Development Lead/New Medicines Therapeutic Area Specialist

Name:	[REDACTED]
Address:	UCB Biopharma SPRL Chemin du Foriest B-1420 Braine-l'Alleud BELGIUM
Phone:	[REDACTED]

---

**Has been changed to:**

Name:	[REDACTED], MD
Address:	UCB Biopharma SPRL Chemin du Foriest B-1420 Braine-l'Alleud BELGIUM
Phone:	[REDACTED]

**Change #3**

**Study Contact Information, Sponsor Study Physician**

Name:	[REDACTED]
Address:	UCB Celltech, UK Registered Branch of UCB Pharma SA 208 Bath Road, Slough Berkshire, SL1 3WE UNITED KINGDOM
Phone:	[REDACTED]

**Has been changed to:**

Name:	[REDACTED], MD
Address:	UCB Biopharma SPRL Chemin du Foriest B-1420 Braine-l'Alleud BELGIUM
Phone:	[REDACTED]

**Change #4**

**Sponsor Contact Information, Clinical Trial Biostatistician**

Name:	[REDACTED]
Address:	UCB Biopharma SPRL Chemin du Foriest B-1420 Braine-l'Alleud BELGIUM
Phone:	[REDACTED]

---

**Has been changed to:**

Name:	
Address:	UCB BIOSCIENCES Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	

**Change #5****List Of Abbreviations****Have been added:**

ANOVA	analysis of variance
PDILI	potential drug-induced liver injury
SAP	Statistical Analysis Plan

**Change #6****Section 1 SUMMARY, bullet #7**

- An echocardiogram during dosing, after the last dose, and at 6 months after the final dose

**Has been changed to:**

- An echocardiogram during dosing and after the last dose (the SFU7 echocardiogram). The echocardiogram will be repeated at 6 months ( $\pm 1$  month) after the last dose in the following subjects:
  - Subjects who complete this study but do not enter the OLE study
  - Subjects who withdraw from the Outpatient Period
  - Subjects who withdraw from the Inpatient Period and have an abnormal SFU7 echocardiogram

**Change #7****Section 3.3 Exploratory objectives****Added the following exploratory objective:**

- To assess motivations, hopes and impact of seizures using a Diary Addendum

**Change #8****Section 4.3 Exploratory variables****Added the following exploratory variable:**

- Responses to open questions in the Diary Addendum, including:
  - Reason for participation in the study
  - Hopes for this new treatment and fulfillment of hopes during the study
  - Baseline and change from Baseline in the impact of seizures on the patient's life

The subject will be instructed to leave any questions blank that he/she does not feel comfortable answering.

## Change #9

### Section 5.1 Study description, bullet #7

- An echocardiogram during dosing, after the last dose, and at 6 months after the last dose

#### Has been changed to:

- An echocardiogram during dosing and after the last dose (the SFU7 echocardiogram). The echocardiogram will be repeated at 6 months ( $\pm 1$  month) after the last dose in the following subjects:
  - Subjects who complete this study but do not enter the OLE study
  - Subjects who withdraw from the Outpatient Period
  - Subjects who withdraw from the Inpatient Period and have an abnormal SFU7 echocardiogram

## Change #10

### Section 5.1 Study description, paragraph immediately following bulleted list (bolded text has been deleted)

UCB0942 doses for placebo subjects will be titrated to UCB0942 400mg bid during the Inpatient Transition-to-Outpatient Week (Day TTO1 to Day TTO7). After the Inpatient Period, all subjects will continue in an open-label Outpatient Maintenance Period and a final Tapering Period of 2 weeks (Day TOO1 to Day TOO14). Doses for subjects continuing in the OLE study will not be tapered but will follow the schedule of safety and efficacy assessments as outlined in the OLE study protocol. Safety follow up will consist of 2 required visits, 1 and 4 weeks after the last dose of IMP (Day SFU7 and Day SFU28), and 1 optional visit 2 weeks after the last dose of IMP (Day SFU14). **In addition, all subjects who do not enter the OLE study will have an echocardiogram 6 months after the last dose of IMP.** For details of the study assessments, refer to Table 5-4. For a general presentation of the study design refer to Figure 5-1.

#### Has been changed to:

UCB0942 doses for placebo subjects will be titrated to UCB0942 400mg bid during the Inpatient Transition-to-Outpatient Week (Day TTO1 to Day TTO7). After the Inpatient Period, all subjects will continue in an open-label Outpatient Maintenance Period and a final Tapering Period of 2 weeks (Day TOO1 to Day TOO14). Doses for subjects continuing in the OLE study will not be tapered but will follow the schedule of safety and efficacy assessments as outlined in the OLE study protocol. Safety follow up will consist of 2 required visits, 1 and 4 weeks after the last dose of IMP (Day SFU7 and Day SFU28), and 1 optional visit 2 weeks after the last dose of IMP (Day SFU14). For details of the study assessments, refer to Table 5-4. For a general presentation of the study design refer to Figure 5-1.

## Change #11

### Section 5.1 Study description, starting at second paragraph following the bulleted list

During the Titration Week the dose for subjects randomized to UCB0942 will be titrated to UCB0942 400mg bid following the schedule in Table 5-1. Subjects randomized to placebo



will follow the same schedule during the Transition-to-Outpatient Week. The entire Inpatient Period will be double-blind.

**Table 5-1: Dose titration to UCB0942 400mg bid**

	Day T1 <sup>a</sup>	Day T2	Day T3	Day T4	Day T5	Day T6	Day T7	Day MD1
AM	0	100mg	100mg	200mg	200mg	300mg	300mg	400mg
PM	100mg	100mg	200mg	200mg	300mg	300mg	400mg	400mg

AM=morning dose; PM=evening dose

<sup>a</sup> In placebo-arm subjects the same schedule is used from Day TTO1 to TTO7.

If a subject is not tolerating UCB0942 400mg bid well, the dose can be tapered to UCB0942 200mg bid. The taper from UCB0942 400mg bid to UCB0942 200mg bid will occur over 3 days (see Table 5-1) and will require unblinding of the subject if this occurs during the Inpatient Period. Dose tapering to UCB0942 100mg bid may be permitted after discussion with the Sponsor's Study Physician.

**Table 5-2: Taper from UCB0942 400mg bid to UCB0942 200mg bid**

	Day TTO1	Day TTO2	Day TTO3	Day TTO4 onwards
AM	300mg	300mg	200mg	200mg
PM	400mg	300mg	300mg	200mg

AM=morning dose; PM=evening dose

At the end of the Outpatient Maintenance Period, or at the time a subject is withdrawn from the study, UCB0942 will be tapered following the schedule in Table 5-3.

**Table 5-3: Dose taper from UCB0942 400mg bid**

Day	TTO1 to TTO4	TTO5 to TTO8	TTO9 to TTO12	TTO13 and TTO14
AM	300mg	200mg	100mg	
PM	300mg	200mg	100mg	100mg

AM=morning; PM=evening dose

In order to provide an ongoing assessment of the safety of subjects as the study progresses, a Safety Review Group (SRG) comprising appropriate Sponsor study team members and the Investigator(s) at each site will meet regularly to review appropriate safety data (see Section 11.1.9).

## **Has been changed to:**

### Dosing in the Inpatient Period

#### *Titration Week (first week of the Inpatient Period)*

The objective of the Titration Week is to achieve the maximum UCB0942 dose of 400mg bid in as many of the subjects randomized to UCB0942 as possible while minimizing tolerability issues. During the Titration Week the dose for subjects randomized to UCB0942 will be titrated to UCB0942 400mg bid following the schedule in Table 5-1. The UCB0942 dose will be titrated to 400mg bid in a double-blinded fashion (ie, it will also appear that subjects randomized to placebo are being titrated). If, in the opinion of the Investigator, the Subject

will be unable to titrate to the maximum dose of IMP due to intolerance of a lower dose, the Investigator should discuss this immediately with the Sponsor Study Physician, unless the subject's condition warrants immediate unblinding, and time does not allow discussion with the Sponsor. Unblinding may be required depending on the plan agreed upon by the Investigator and Sponsor Study Physician before dose tapering to UCB0942 200mg bid or 100mg bid. If unblinding reveals that the Subject is randomized to placebo, then further dosing with IMP will cease until the Transition-to-Outpatient Week (third week of the Inpatient Period), at which time, the Subject will titrate UCB0942 according to Table 5-1. All other assessments will continue as planned.

**Table 5-1: Dose titration to UCB0942 400mg bid**

	Day T1 <sup>a</sup>	Day T2	Day T3	Day T4	Day T5	Day T6	Day T7	Day MD1
AM	0	100mg	100mg	200mg	200mg	300mg	300mg	400mg
PM	100mg	100mg	200mg	200mg	300mg	300mg	400mg	400mg

AM=morning dose; PM=evening dose

<sup>a</sup> In placebo-arm subjects the same schedule is used from Day TTO1 to TTO7.

*Maintenance-Dose Week (second week of the Inpatient Period)*

If a subject is not tolerating the maximum dose of IMP well during the Maintenance-Dose Week such that the Investigator believes a dose reduction is necessary, then the Investigator should contact the Sponsor Study Physician to discuss the situation and agree upon a course of action. If a dose reduction is agreed, unblinding will be required. If the subject is randomized to UCB0942, the dose can be tapered from UCB0942 400mg bid to UCB0942 200mg bid. The taper from UCB0942 400mg bid to UCB0942 200mg bid will occur over 3 days (see Table 5-2). Dose tapering to UCB0942 100mg bid may also be permitted after discussion with the Sponsor's Study Physician. If it is revealed that the Subject is randomized to placebo, then further dosing with IMP will cease until the Transition-to-Outpatient Week (third week of the Inpatient Period), at which time, the Subject will titrate UCB0942 according to Table 5-1. All other assessments will continue as planned.

**Table 5-2: Taper from UCB0942 400mg bid to UCB0942 200mg bid**

	Taper Day 1	Taper Day 2	Taper Day 3	Taper Day 4 onwards
AM	300mg	300mg	200mg	200mg
PM	400mg	300mg	300mg	200mg

AM=morning dose; PM=evening dose

*Transition-to-Outpatient Week (third week of the Inpatient Period)*

The objective of the Transition-to-Outpatient Week is to achieve the maximum UCB0942 dose of 400mg bid in as many of the subjects randomized to placebo (now switching to UCB0942) as possible while minimizing tolerability issues. The UCB0942 dose will be titrated to 400mg bid in a double-blinded fashion (ie, it will also appear that subjects randomized to UCB0942 are being titrated) following the schedule in Table 5-1. If, in the opinion of the Investigator, the Subject will be unable to titrate to the maximum dose of IMP due to intolerance of a lower dose, the Investigator should discuss this with the Sponsor

Study Physician. Unblinding may be required depending on the plan agreed upon by the Investigator and Sponsor Study Physician.

#### Dosing in the Outpatient Maintenance Period and Tapering Period

During the Outpatient Maintenance Period, Subjects will continue to administer UCB0942 at the final Inpatient Period dose. Multiple adjustments (tapering or increase) of the dose are allowed during the Outpatient Maintenance Period (minimum 100mg bid and maximum 400mg bid); however, any change of dose in the Outpatient Maintenance Period should first be discussed with the Sponsor Study Physician.

At the end of the Outpatient Maintenance Period, or at the time a subject is withdrawn from the study, UCB0942 will be tapered following the schedule in Table 5-3. If the subject is not taking a dose of UCB0942 other than 400mg bid, then the Investigator should contact the Sponsor Study Physician to discuss the appropriate tapering schedule.

**Table 5-3: Dose taper from UCB0942 400mg bid**

Day	TOO1 to TOO4	TOO5 to TOO8	TOO9 to TOO12	TOO13 and TOO14
AM	300mg	200mg	100mg	
PM	300mg	200mg	100mg	100mg

AM=morning; PM=evening dose

In order to provide an ongoing assessment of the safety of subjects as the study progresses, a Safety Review Group (SRG) comprising appropriate Sponsor study team members and the Investigator(s) at each site will meet regularly to review appropriate safety data (see Section 11.1.9).

#### **Change #12**

#### **Section 5.2 Schedule of study assessments, Table 5-4**

#### **Added the following assessment:**

Diary Addendum has been added. This is completed at V3 and V15.

#### **Change #13**

#### **Section 5.2 Schedule of study assessments, Table 5-4, footnote k**

In addition to the echocardiogram during dosing and after the last dose, for subjects who do not continue in the OLE study, an echocardiogram at 6 months after the last dose will also be performed. Please note that the during dosing time point of Day OP22 for the echocardiogram has a time window of  $\pm 1$  week instead of  $\pm 2$  days.

#### **Has been changed to:**

In addition to the echocardiogram during dosing and after the last dose (SFU7), the echocardiogram will be repeated at 6 months ( $\pm 1$  month) after the last dose in the following subjects: 1) Subjects who complete this study but do not enter the OLE study, 2) Subjects who withdraw from the Outpatient Period, and 3) Subjects who withdraw from the Inpatient Period and have an abnormal SFU7 echocardiogram. Please note that the during dosing time point of Day OP22 for the echocardiogram has a time window of  $\pm 1$  week instead of  $\pm 2$  days and the Day SFU7 echocardiogram has a time window of  $\pm 1$  week instead of  $\pm 1$  day.

## **Change #14**

### **Section 5.2 Schedule of study assessments, Table 5-4, new footnote x**

#### **Added the following footnote x (pertaining to the Diary Addendum):**

The subject will be instructed to leave any questions blank that he/she does not feel comfortable answering

## **Change #15**

### **Section 5.2 Schedule of study assessments, Table 5-4, new footnote y**

#### **Added the following footnote y (pertaining to the Diary Addendum):**

Collect at Day OP57 or at Early Withdrawal.

## **Change #16**

### **Section 5.2 Schedule of study assessments, Inpatient Period Table 5-5**

#### **Added the following assessment:**

Diary Addendum has been added. This is completed at V3, Study Day T1.

## **Change #17**

### **Section 5.2 Schedule of study assessments, Inpatient Period Table 5-5, new footnote o**

#### **Added the following footnote o (pertaining to the Diary Addendum):**

The subject will be instructed to leave any questions blank that he/she does not feel comfortable answering.

## **Change #18**

### **Section 6.1 Inclusion criteria, Inclusion Criterion #5 (changes bolded)**

Subject is of normal weight as determined by a body mass index (BMI) between **18.0** and **35.0kg/m<sup>2</sup>** (exclusive), with a body weight of at least 50kg (males) or 45kg (females).

#### **Has been changed to:**

Subject is of normal weight as determined by a body mass index (BMI) between **16.0** and **40.0kg/m<sup>2</sup>** (exclusive) and with a body weight of at least 50kg (males) or 45kg (females).

## **Change #19**

### **Section 6.2 Exclusion criteria, Exclusion Criterion #2**

Subject has a history of liver disease, including but not limited to, stable (on repeat testing) elevation of liver enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >1.5 times the upper limit of laboratory reference ranges or alkaline phosphatase [ALP] >2 times the upper limit of laboratory reference range).

#### **Has been changed to:**

Subject has either:

- >1.5x upper limit of normal (ULN) of any of the following:
  - alanine aminotransferase (ALT)

- aspartate aminotransferase (AST)
- alkaline phosphatase (ALP)

**-OR-**

- >ULN total bilirubin ( $\geq 1.5 \times$ ULN total bilirubin if known Gilbert's syndrome).

If subject has elevations only in total bilirubin that are >ULN and  $< 1.5 \times$ ULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin  $< 35\%$ ).

For randomized subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the Case Report form (CRF).

If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

**Change #20 Exclusion criteria, Exclusion Criterion #14 (changes bolded)**

Subject is currently treated with carbamazepine, phenytoin, primidone, or phenobarbital or any other drug known to induce CYP3A4 liver enzymes.

**Has been changed to:**

Subject is currently treated with carbamazepine, phenytoin, primidone, or phenobarbital or any other drug known as a **strong inducer** of CYP3A4 liver enzymes.

**Change #21**

**Section 6.3 Withdrawal criteria, Withdrawal Criterion #1**

Subject develops a clinically relevant medical condition (or laboratory abnormality) that, in the opinion of the Investigator, compromises the subject's ability to participate or safety. In the case of transaminase (AST, ALT, or both) levels at least 3 times the upper limit of normal (ULN) in the presence of normal total bilirubin, the laboratory tests will be repeated within a few days. If the repeat testing confirms the abnormality, then weekly monitoring of liver function tests should continue until resolved (ie, less than 3 times the ULN or stable condition). The Investigator is to decide whether or not to stop the investigational medicinal product (IMP). To monitor for hypersensitivity reactions, percent eosinophils  $> 10\%$  or absolute eosinophil count  $\geq 0.5 \text{ G/L}$  or absolute neutrophil count  $< 1.5 \text{ G/L}$  or absolute platelet count  $\leq 100 \text{ G/L}$ , if in combination with fever, rash, lymphadenopathy, or other symptoms/signs suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, or arthritis) will lead to stopping the IMP.

**Has been changed to:**

Subject develops a clinically relevant medical condition (or laboratory abnormality) that, in the opinion of the Investigator, compromises the subject's ability to participate or safety. Potential drug-induced liver injury IMP discontinuation criteria are described in Section 6.3.1. To monitor for hypersensitivity reactions, percent eosinophils  $> 10\%$  or absolute eosinophil count  $\geq 0.5 \text{ G/L}$  or absolute neutrophil count  $< 1.5 \text{ G/L}$  or absolute platelet count  $\leq 100 \text{ G/L}$ , if in combination with fever, rash, lymphadenopathy, or other symptoms/signs suggestive of internal organ involvement (including but not limited to hepatitis, nephritis,



pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, or arthritis) will lead to stopping the IMP.

## **Change #22**

### **Section 6.3 Withdrawal criteria, Withdrawal Criterion #6**

Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response (Yes) to either Question 4 or Question 5 of the C-SSRS at Screening. Subjects may be withdrawn from the study if the following event occurs: for subject who did not complete a C-SSRS at Screening, subject had actual suicidal ideation prior to study entry or since study initiation as indicated by a positive response (Yes) to either Question 4 or Question 5 of the "Already Enrolled Subjects" version of the C-SSRS. The Investigator must immediately refer the subject to a Mental Healthcare Professional and use clinical judgment as to whether to withdraw the subject from the study.

#### **Has been changed to:**

Subject has active suicidal ideation without specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and may be withdrawn from the study based upon the Investigator's judgment of benefit/risk of continuing the subject in the study/on study medication. If the Subject has active suicidal ideation with a plan as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS, the subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

## **Change #23**

### **Section 6.3 Withdrawal criteria**

#### **Added the following Withdrawal Criterion #7:**

Subject has a prolongation or worsening of overall seizure duration, frequency, type, or pattern considered by the Investigator as persistent and serious enough to warrant discontinuation from the study.

## **Change #24**

### **Section 6.3 Withdrawal criteria, paragraph immediately above Section 6.3.1**

The Investigator should contact the UCB Study Physician whenever possible to discuss the withdrawal of a subject in advance.

#### **Has been changed to:**

The Investigator should contact the UCB Study Physician whenever possible to discuss the withdrawal of a subject in advance. If this is not possible, the Investigator should contact the UCB study physician to inform him/her about the subject withdrawal as soon as possible after the withdrawal.



## Change #25

### Section 6.3 Withdrawal criteria

#### Added Section 6.3.1 Potential drug-induced liver injury IMP discontinuation criteria:

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST  $\geq 5 \times \text{ULN}$
  - ALT or AST  $\geq 3 \times \text{ULN}$  and coexisting total bilirubin  $\geq 2 \times \text{ULN}$

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST  $\geq 3 \times \text{ULN}$  who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie,  $>5\%$ ).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 11.6.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

- Subjects with ALT or AST  $\geq 3 \times \text{ULN}$  (and  $\geq 2 \times$  baseline) and  $< 5 \times \text{ULN}$ , total bilirubin  $< 2 \times \text{ULN}$ , and no eosinophilia (ie,  $\leq 5\%$ ), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 11.6.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The CRF must document the primary reason for IMP discontinuation.

## Change #26

### Section 7.1 Description of investigational medicinal products, Table 7-1 (bolded text in Note has been revised)

**Table 7-1: Description of investigational medicinal product**

	UCB0942	Placebo for UCB0942
Dosage form	Tablets (white, film-coated), in 2 strengths: - 100mg - 200mg  100mg and 200mg tablets have the same size and appearance	Tablets (white, film-coated): Provided in a size and appearance matching UCB0942.
Manufacturer	[REDACTED]	
Batch/lot number	Will be assigned according to GMP	
Expiry date	Will be assigned according to GMP	

GMP=Good Manufacturing Practice

Note: For the Inpatient Period, 1 kit per treatment period and per dose will be packaged. Each kit will contain blister packs, each covering 1 week of treatment. For the Outpatient Period, UCB0942 tablets will be provided in bottles, containing 37 tablets per bottle, either 200mg tablets for subjects on UCB0942 400mg bid, or 100mg tablets for subjects who reduce dose to UCB0942 **200mg** bid. The bottles containing 37 UCB0942 100mg tablets will be dispensed for the Taper Period.

**Has been changed to (bolded text in table and in Note has been added):**

**Table 7-1: Description of investigational medicinal product**

	<b>UCB0942</b>	<b>Placebo for UCB0942</b>
Dosage form	Tablets (white, film-coated), in 2 strengths: - 100mg - 200mg  100mg and 200mg tablets have the same size and appearance	Tablets (white, film-coated): Provided in a size and appearance matching UCB0942.
Manufacturer	[REDACTED]	
Batch/lot number	Will be assigned according to GMP	
Expiry date	Will be assigned according to GMP	

GMP=Good Manufacturing Practice

Note: For the Inpatient Period, 1 kit per treatment period and per dose will be packaged. Each kit will contain blister packs, each covering 1 week of treatment. For the Outpatient Period, UCB0942 tablets will be provided in bottles, containing 37 tablets per bottle, either 200mg tablets for subjects on UCB0942 400mg bid or **UCB0942 200mg bid**, or 100mg tablets for subjects who reduce dose to UCB0942 **100mg bid**. The bottles containing 37 UCB0942 100mg tablets will be dispensed for the Taper Period.

## Change #27

### Section 7.9.1.3 Breaking the treatment blind for taper of dose during the study

If the IMP is not tolerated during the Inpatient Period by an individual subject, the dose can be tapered to UCB0942 200mg bid. This is only permitted if the subject has great difficulty tolerating the IMP and the Investigator does not think that tolerability will improve. When it is decided to reduce the dose, the blind will have to be broken, following the procedure described in Section 7.9.1.2.

#### **Has been changed to:**

When the Investigator and Sponsor Study Physician agree that a subject cannot titrate to the maximum dose or that a dose reduction is necessary during the Inpatient Period (See Section 5.1, the blind will have to be broken, following the procedure described in Section 7.9.1.2.

## Change #28

### Section 8.2.1 Titration Week (Visit 3, Day T1 to Day T7)

#### Added the following assessment:

- Diary Addendum (T1)

## Change #29

### Section 8.3.1 Outpatient Maintenance Period (Visit 6 to Visit 15, Day OP1 to Day OP57)

#### Added the following assessment:

- Diary Addendum (OP57)

## Change #30

### Section 8.3.3 Safety Follow-Up (Visit 18 to 20, Day SFU7, SFU14, and SFU28), bullet #8

- Echocardiogram after last dose and 6 months later ( $\pm 1$  month)

#### Has been changed to:

- Echocardiogram after last dose and 6 months later ( $\pm 1$  month). For subjects who withdraw during the Inpatient Period and for subjects who withdraw during the Outpatient Period, see Section 8.4 for echocardiogram requirements following withdrawal.

## Change #31

### Section 8.3.4 Echocardiograph follow up

For subjects who do not continue in the OLE study, it is mandatory that they have an echocardiogram at 6 months ( $\pm 1$  month) after the last dose of IMP (in addition to the echocardiogram at Screening, during dosing, and after the last dose).

#### Has been changed to (bolded text added):

For subjects **who complete this study** but do not continue in the OLE study, it is mandatory that they have an echocardiogram at 6 months ( $\pm 1$  month) after the last dose of IMP (in addition to the echocardiogram at Screening, during dosing, and after the last dose).

## Change #32

### Section 8.4 Withdrawal Visit, bullet #6

- Echocardiogram after last dose and 6 months later ( $\pm 1$  month)

#### Has been changed to:

- Echocardiogram
  - Withdrawal during the Inpatient Period: The SFU7 echocardiogram should be performed. If there is no abnormality, the echocardiogram does not need to be repeated. If there is an abnormality, the echocardiogram should be repeated at 6 months ( $\pm 1$  month) after the last dose of IMP.

- Withdrawal during the Outpatient Period: The SFU7 echocardiogram should be performed, and the echocardiogram should be repeated at 6 months ( $\pm 1$  month) after the last dose of IMP.

### **Change #33**

#### **Section 8.4 Withdrawal Visit**

##### **Added the following assessment:**

- Diary Addendum

### **Change #34**

#### **Section 9.4 Diary Addendum**

##### **This Section has been added:**

A Diary Addendum will be completed according to the tabular schedule of study procedures in Table 5-4 as well as at the Withdrawal Visit, if applicable. The Diary Addendum will consist of a series of open-ended questions including the following:

- Why did you agree to take part in this study?
- What are your hopes for this new treatment?
- What are the biggest impacts of seizures on your life currently?
- What was your experience like during the study?
- Did participating in the study fulfill any of the hopes you had going into the study?
- How do you describe the impact of seizures on your life now? Has that changed since the beginning of the study?

Subjects will be instructed to leave any question blank that he/she does not feel comfortable answering.

### **Change #35**

#### **Section 11.3 Adverse events of special interest**

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

There are no adverse events of special interest to be reported for UCB0942.

##### **Has been changed to:**

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Potential Hy's Law, defined as  $\geq 3 \times \text{ULN}$  ALT or AST with coexisting  $\geq 2 \times \text{ULN}$  total bilirubin in the absence of  $\geq 2 \times \text{ULN}$  ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

## Change #36

### Section 11.7.3 Echocardiograms

Echocardiograms will be performed during Screening, during dosing (Day OP22  $\pm$ 1 week), after the last dose of IMP, and at 6 months after the last dose of IMP, as described in Table 5-4.

2D Doppler echocardiography will be performed with:

1. Diastolic measurements (mitral forward flow E and A waves and deceleration time)
2. Tissue Doppler on medial and lateral mitral valve annulus (S, E, and A waves)
3. Standardized views for left atrial volume measurements

Images will be recorded and stored digitally and retained if further analysis is needed. A complete echocardiography manual will be provided.

#### Has been changed to:

Echocardiograms will be performed during Screening, during dosing (Day OP22  $\pm$ 1 week), and after the last dose of IMP (SFU7), as described in Table 5-4. The echocardiogram will be repeated at 6 months ( $\pm$ 1 month) after the last dose in the following subjects:

- Subjects who complete this study but do not enter the OLE study
- Subjects who withdraw from the Outpatient Period
- Subjects who withdraw from the Inpatient Period and have an abnormal SFU7 echocardiogram

2D Doppler echocardiography will be performed with:

1. Diastolic measurements (mitral forward flow E and A waves and deceleration time)
2. Tissue Doppler on medial and lateral mitral valve annulus (S, E, and A waves)
3. Standardized views for left atrial volume measurements

Images will be recorded and stored digitally and retained if further analysis is needed. A complete echocardiography manual will be provided.

## Change #37

### Section 11.6 Laboratory assessments

#### Added Section 11.6.1 Evaluation of PDILI:

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 11.3), and, if applicable, also reported as an SAE (see Section 11.1.1).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11-3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.6.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a



gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.6.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable CRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 11.6.1.2.1 are met, rechallenge with IMP may be appropriate.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

**Table 11-3: Required investigations and follow up for PDILI**

Laboratory value		Symptoms <sup>a</sup> of hepatitis or hypersensitivity	Immediate		Follow up	
ALT or AST	Total bilirubin		Consultation requirements	Actions	Testing	Evaluation
≥3xULN	≥2xULN <sup>b</sup>	NA	Hepatology consult. <sup>c</sup> Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.6.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values. <sup>d</sup>
≥8xULN	NA	NA		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN	NA	Yes		Further investigation – immediate IMP discontinuation not required (see Section 11.6.1.2).		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 11.6.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values. <sup>d</sup>

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner;

IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

<sup>a</sup> Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

<sup>b</sup> If the subject also has  $\geq 2 \times$  ULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

<sup>c</sup> Details provided in Section 11.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

<sup>d</sup> Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed

#### **11.6.1.1 Consultation with the Medical Monitor and local hepatologist**

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 11.6.1.3) and SAE report (if applicable).

#### **11.6.1.2 Immediate action: determination of IMP discontinuation**

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 11-3 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

##### **11.6.1.2.1 IMP restart/rechallenge (if applicable)**

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 11-3), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 11.6.1.3 and Section 11.6.1.4 confirm a non-drug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed  $\geq 3 \times \text{ULN}$ .
- Subject's total bilirubin is  $< 1.5 \times \text{ULN}$ .
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician and a hepatologist. The hepatologist must be external to UCB. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the investigator-recommended monitoring plan.

#### **11.6.1.3 Testing: identification/exclusion of alternative etiology**

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed

in Table 11-4 (laboratory measurements) and Table 11-5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding CRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

**Table 11-4: PDILI laboratory measurements**

<b>Virology-related</b>	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
<b>Immunology</b>	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
<b>Hematology</b>	Eosinophil count
<b>Urinalysis</b>	Toxicology screen
<b>Chemistry</b>	Amylase
	If total bilirubin $\geq 1.5 \times \text{ULN}$ , obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
<b>Additional</b>	Prothrombin time/INR <sup>a</sup>
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

<sup>a</sup> Measured only for subjects with ALT  $> 8 \times \text{ULN}$ , elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia ( $> 5\%$ ), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

**Table 11-5: PDILI information to be collected**

<b>New or updated information</b>
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: <ul style="list-style-type: none"><li>• History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other “fatty liver disease”)</li><li>• Adverse reactions to drugs</li><li>• Allergies</li><li>• Relevant family history or inheritable disorders (eg, Gilbert’s syndrome, alpha-1 antitrypsin deficiency)</li><li>• Recent travel</li><li>• Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)</li></ul>
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

#### **11.6.1.4 Follow-up evaluation**

Potential drug-induced liver injury events require follow-up and monitoring as described in Table 11–3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

#### **Change #38**

#### **Section 11.7.5 Assessment of suicidality**

Suicidality will be assessed by trained study personnel using the C-SSRS (Posner et al, 2011). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures (Section 5.2)

#### **Has been changed to (bolded text added):**

Suicidality will be assessed by trained study personnel using the C-SSRS (Posner et al, 2011). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures (Section 5.2). **The Investigator’s decision about patient continuation in the study or patient withdrawal from the study if the patient has a positive response to the CSSRS Question 4, should be based on the Benefit /Risk balance for continuation**



**or discontinuation of study treatment in view of the individual patient circumstances, condition, attained efficacy, causality, alternative risk management options, etc. Details of the case must be documented by the investigator (PI or investigator physician, not site staff conducting the CSSRS) and provided to UCB via the SAE reporting process.**

## **Change #39**

### **Section 13.7 Planned interim analyses and data monitoring**

#### **This Section has been added:**

An interim analysis will be performed if needed for purposes of planning and designing of future studies. If performed, this analysis will be conducted when at least 75% of patients have been randomized and completed through the Inpatient Period (completed through Visit 5).

All subjects who have completed through Visit 5 at the time of the data snapshot will be included in the interim analysis.

All statistical analyses will be described in detail in the interim SAP.

For the interim analysis, the primary efficacy variable (75%RR) will be analyzed using the methods described for the primary efficacy analysis. In addition, seizure-free rate, 50%RR, and percent reduction in focal seizure frequency will be analyzed as described for the secondary/exploratory analyses.

The 75%RR, Seizure-free rate, and 50%RR variables may also be analyzed using Bayesian logistic regression. If Bayesian analysis is performed, the percent reduction in focal seizure frequency from the Baseline will be estimated using Bayesian analysis of variance (ANOVA) and/or ANCOVA. For these analyses, posterior medians, 95% credible intervals for the treatment effect, and additional posterior probabilities will be presented. Non informative and informative priors will be considered, and sensitivity to different prior settings will be assessed. Other efficacy variables may also be analyzed in the Bayesian framework.

The following safety data will also be presented:

- Treatment emergent AEs
- AEs leading to drop-out or withdrawal
- SAEs
- Laboratory assessments out of normal range
- BPRS

The study will not be terminated early for either efficacy or futility based on the results of this interim analysis and therefore, an alpha penalty of 0.001 to be assessed on the primary efficacy analysis is considered appropriate.

The study is not expected to be stopped due to safety reasons during this interim analysis, since there are ongoing quarterly Safety Review Group meetings already planned for this purpose. Therefore, no criteria for evaluation of early stopping due to safety are included.

An unblinded team will be established at both the Sponsor and CRO and will include the following roles (all unblinded): Data Manager, Statistician, Statistical Programmer, and Project Lead. All staff involved in the conduct of the study, including staff at UCB, the CRO, participating vendors, and the participating sites will remain blinded to individual treatment identity and will not be informed of the results of the interim analysis until final unblinding.

## 17.4 Protocol Amendment 4.0

### Rationale for the Amendment

The primary reason for Amendment 4.0 is to describe a tiered approach to database lock and unblinding.

Other changes include:

- Correction of an inconsistency between the Summary section and the Study Design section pertaining to allowable dose changes
- Clarification of the reporting period for adverse events
- Specification that the Baseline version of the SSQ is to be used in all instances where it is administered
- Correction of the number of questions in the SSQ was from 11 to 10.
- Correction of several cross references
- Other minor administrative changes

### Modifications and changes

#### Specific changes

##### Change #1

#### Summary (revised for consistency with Section 5, Study Design)

Titration to UCB0942 400mg bid will occur over the course of 1 week in the clinical unit. For subjects in the active arm, doses will be titrated to UCB0942 400mg bid during the first inpatient week. For subjects who initially received placebo, doses will be titrated to UCB0942 400mg bid during the last week of the Inpatient Period. For subjects in the active arm who do not tolerate UCB0942 400mg bid, during the third week of the Inpatient Period, the dose can be tapered to UCB0942 200mg bid before starting the Outpatient Maintenance Period. Similarly, for subjects in the placebo group the dose can be tapered to UCB0942 200mg bid during the Outpatient Maintenance Period. Dose tapering to UCB0942 100mg bid may be permitted after discussion with the Sponsor's Study Physician. All subjects will stay in the clinical unit for a total of 3 weeks and will then be discharged for an 8-week Outpatient Maintenance Period.

#### Has been changed to:

Titration to UCB0942 400mg bid will occur over the course of 1 week in the clinical unit. For subjects in the active arm, doses will be titrated to UCB0942 400mg bid during the first inpatient week. For subjects who initially received placebo, doses will be titrated to UCB0942 400mg bid during the last week of the Inpatient Period. Dose reductions will be allowed during titration and maintenance in the Inpatient Period, but this should be discussed with the Sponsor Study Physician unless this is not possible due to the circumstances. Multiple adjustments (tapering or increase) of the dose are allowed during the Outpatient Maintenance Period (minimum 100mg bid and maximum 400mg bid); however, any change of dose in the Outpatient Maintenance Period should first be discussed with the Sponsor Study Physician.

## Change #2

### Section 5.1.3 Anticipated regions and countries

The study is planned to be performed in The [REDACTED]. Other countries in the [REDACTED] can be added if deemed necessary by the Sponsor.

#### Has been changed to:

The study is planned to be performed in The [REDACTED] [REDACTED] [REDACTED] [REDACTED] and [REDACTED]

## Change #3

Table 5-4, row header, Table 5-5 row header and footnote m, Section 8 – Study Procedures by Visit: SSQ has been revised to SSQ (Baseline version) to make it clear that whenever the SSQ is administered, the Baseline version is to be used.

## Change #4

Table 5-4, row header had been revised to correct the duration of the Taper and Safety Follow-up Periods. The Taper Period is up to 2 weeks, and the Safety Follow-up Period is 4 weeks.

## Change #5

### Section 9.2 Seizure severity questionnaire

The SSQ (Cramer et al, 2002) is a review of various aspects of seizures. The person who has seizures may ask people who have observed the seizures (family, friends) to help answer some of the questions asking about events, but not about feelings. There are 11 questions in 3 sections asking about events before, during, and after typical seizures.

The subject should describe their most common type of seizure when answering the questions. If subjects are unsure about how to answer a question, they should give the best answer they can and write a comment or explanation on the side of the page.

The SSQ will be completed according to the tabular schedule of study procedures, Table 5-4. For this study the recall period will be set to 1 week rather than the original 4 weeks. At the very beginning of the visit, the SSQ will be provided to all subjects. The subject will be asked to complete the questionnaire on his/her own. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the SSQ will be covered in the Study Manual.

#### Has been changed to (changes bolded):

The SSQ (Cramer et al, 2002) is a review of various aspects of seizures. The person who has seizures may ask people who have observed the seizures (family, friends) to help answer some of the questions asking about events, but not about feelings. There are **10** questions in 3 sections asking about events before, during, and after typical seizures.

The subject should describe their most common type of seizure when answering the questions. If subjects are unsure about how to answer a question, they should give the best answer they can and write a comment or explanation on the side of the page.

The **Baseline** SSQ will be completed according to the tabular schedule of study procedures, Table 5-4. The **Baseline version** of the SSQ will be used for all visits during which the SSQ is to be completed. For this study the recall period will be set to 1 week rather than the original 4 weeks. At the very beginning of the visit, the SSQ will be provided to all subjects.

The subject will be asked to complete the questionnaire on his/her own. Once completed, the subject will return the completed questionnaire to the Investigator or designee, who will verify that all questions have been answered. Further details about the SSQ will be covered in the Study Manual.

## Change #6

### Section 11.1.1, Definition of adverse event, paragraph 2

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

#### Has been changed to (change bolded):

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, **ie, through the end of the Taper/Safety Follow-up Period**, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

## Change #7

### Section 11.1.4, Follow up of of adverse events, paragraph 2

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 30 days after the subject has discontinued his/her IMP.

#### Has been changed to (changes bolded):

If an AE is ongoing at the end of **the Taper/Safety Follow-up Period**, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 30 days after the subject has discontinued his/her IMP.

**Adverse events should not be recorded in the eCRF after the end of the Taper/Safety Follow-up Period.**

## Change #8

### Section 11.1.9, Safety Review Group, paragraph 3

The SRG will remain blinded during the study unless emergent safety information requires unblinding of individual drug allocation for optimal assessment and response to AEs of concern.

#### Has been changed to:

The SRG will remain blinded through the first database lock (see Section 12.3.3) unless emergent safety information requires unblinding of individual drug allocation for optimal assessment and response to AEs of concern. At the time of the first database lock, the Study

Physician(s), clinical pharmacologist, DS representative, biostatistician, and other UCB personnel will be unblinded as to all subjects' treatment allocation at the beginning of the Inpatient Period.

## **Change #9**

### **Section 11.6.1, Evaluation of PDILI**

Several incorrect table and section references have been corrected.

## **Change #10**

### **Section 12.3.3, Database lock** – section has been added:

The database lock and unblinding may occur in a tiered approach.

Details regarding the tiered database lock will be described in the Data Management Plan. Plans for analysis of data and production of tables, figures and listings will be described in the Statistical Analysis Plan (SAP).

## **Change #11**

### **Section 13.5, Handling of protocol deviations, paragraph 1**

After all data have been verified/entered into a database and prior to database lock, a data evaluation meeting will take place. The purpose of the data evaluation will be to examine all protocol deviations, define the PPS, and to verify the quality of the data. The data evaluation will also help in guiding decisions on how to manage data issues on a case-by-case basis (eg, withdrawals, dropouts, and protocol deviations).

### **Has been changed to (changes bolded):**

After all **lockable** data have been verified/entered into a database and prior to **the first** database lock, a data evaluation meeting will take place. The purpose of the data evaluation will be to examine all protocol deviations, define the PPS, and to verify the quality of the data. The data evaluation will also help in guiding decisions on how to manage data issues on a case-by-case basis (eg, withdrawals, dropouts, and protocol deviations).

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## 18 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

---

Printed name

---

Date/Signature



## 19 DECLARATION AND SIGNATURE OF COORDINATING INVESTIGATOR ( [REDACTED] )

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Coordinating Investigator ( [REDACTED] )  
[REDACTED]

\_\_\_\_\_  
Date/Signature

---

## 20      **DECLARATION AND SIGNATURE OF COORDINATING INVESTIGATOR**

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Coordinating Investigator:

██████████

\_\_\_\_\_  
Date/Signature

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## 21 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

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EP0069 Protocol Amendment 4.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
	Clinical Approval	13-Oct-2016 15:32 GMT+02
De	Clinical Approval	13-Oct-2016 16:17 GMT+02